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official publication of the American Society of Hospital Pharmacists

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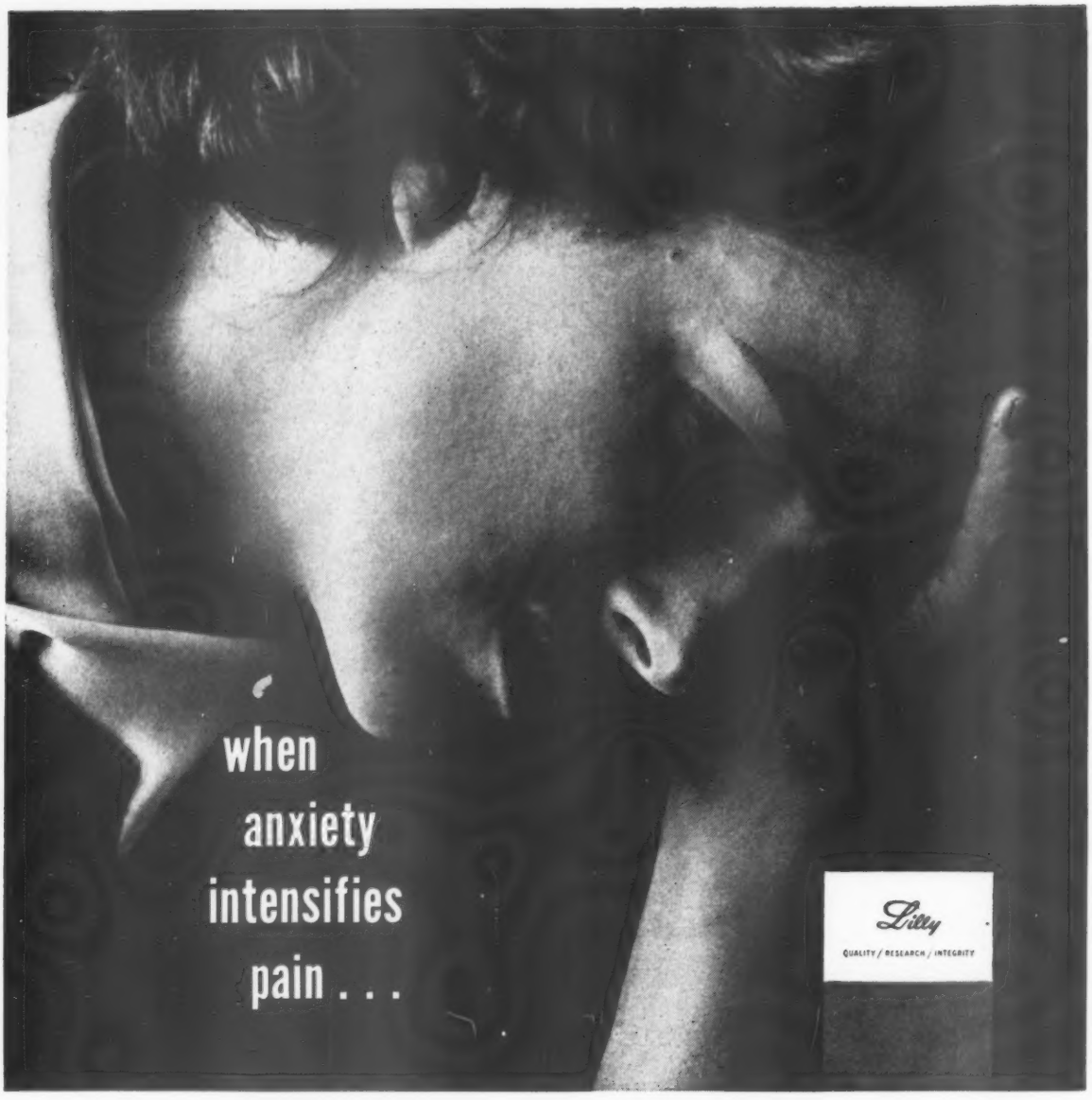

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American Journal of Hospital Pharmacy

American Society of Hospital Pharmacists

VOLUME 17 NUMBER 2 FEBRUARY, 1960

articles

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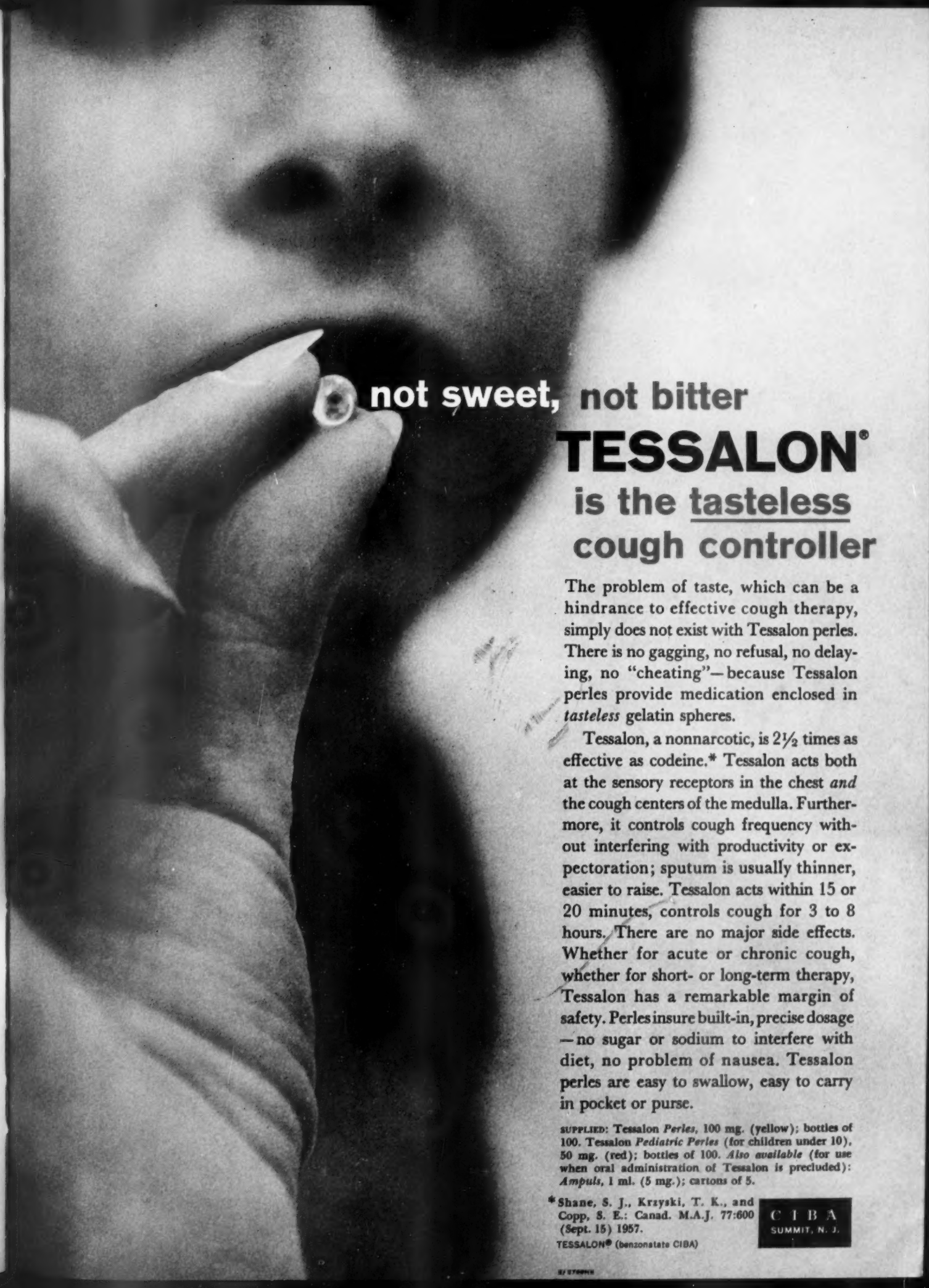

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* Shane, S. J., Krzyski, T. K., and Copp, S. E.: Canad. M.A.J. 77:600 (Sept. 15) 1957.

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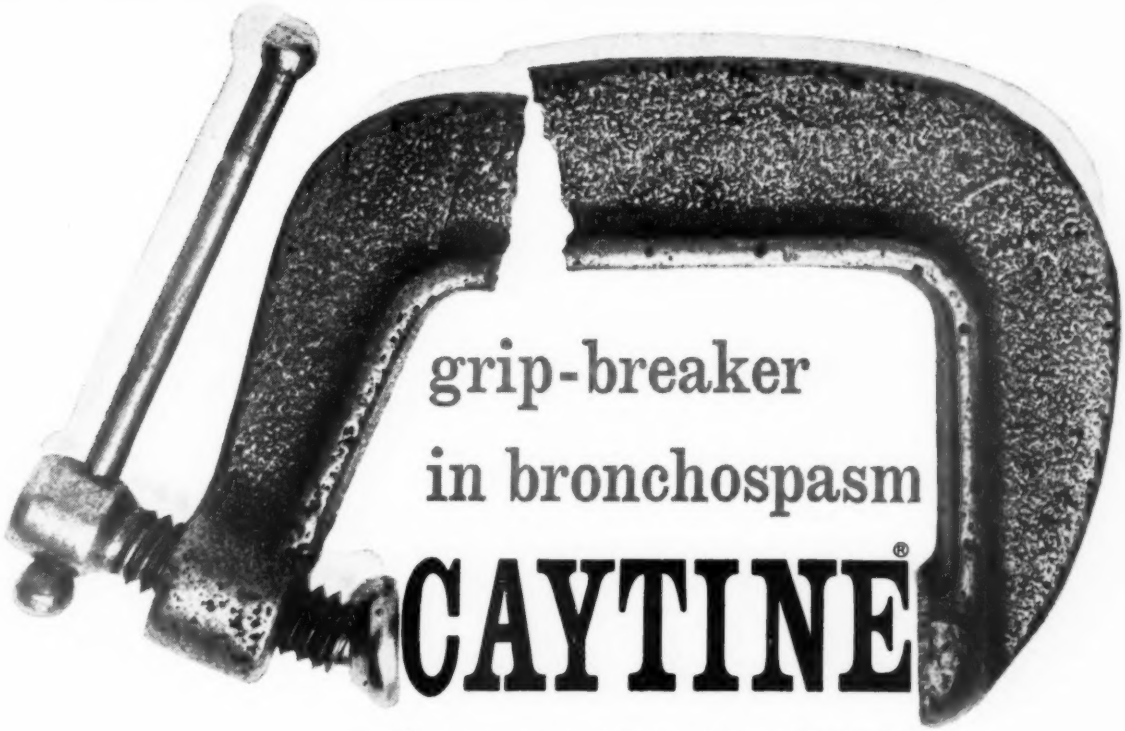

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(1) Leslie, A., and Simmons, D. H.: Am. J. M. Sc. *234*:321, 1957. (2) Settel, E.: Am. Pract. & Digest Treat. *8*:1249, 1957.

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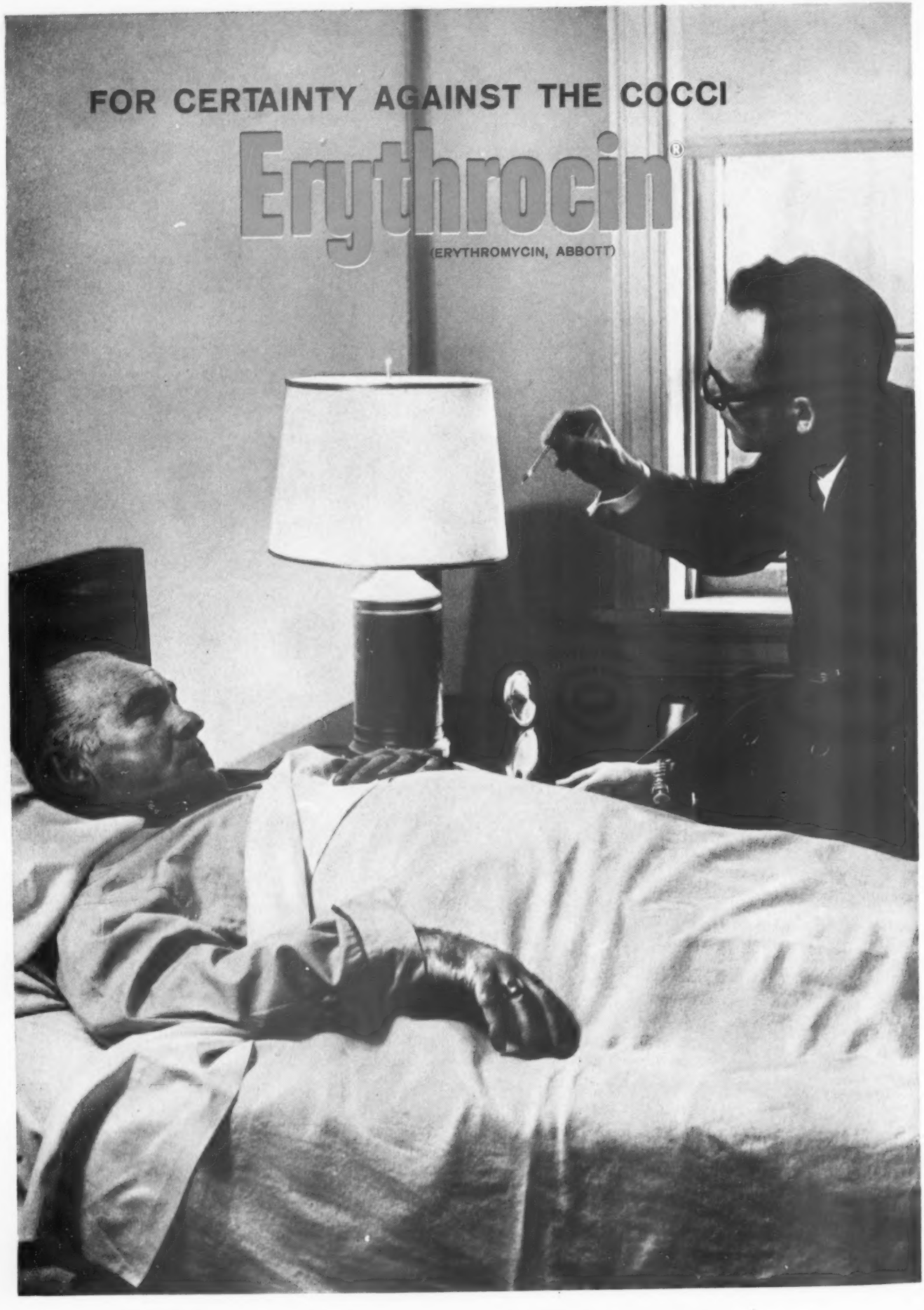
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1. Accurately measured dose assured
2. Danger of giving wrong drug reduced

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3. Efficiency of Central Supply increased
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TUBEX cartridge-needle units are pre-sterilized; the needles pre-sharpened. This means that Central Supply can turn its attention to duties other than the time-consuming sterilization of syringes and the sharpening and sterilization of needles. It also means that breakage, which invariably accompanies these operations, and which raises the hospital's costs, is drastically reduced.

5. A source of hepatitis eliminated
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7. Inventory control simplified
8. Narcotic security tightened

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TUBEX System: cartridge-needle unit, syringe
Conventional System: plunger, barrel, needle, medication

There are fewer records to keep. Inventory control, therefore, is more accurate and efficient. As inventory control becomes more accurate, narcotic security automatically tightens.

9. Patients react more pleasantly to injections
10. Most commonly used drugs available

The most obvious direct benefit that the TUBEX system provides for the patient is a relatively painless injection, the result of a fresh, pre-sharpened, single-use needle. Since most common drugs—and many uncommon ones as well—are available in TUBEX form, the majority of hospital patients can benefit from the TUBEX system.

11. Accounting made more efficient
12. Billing made more accurate

Since each cartridge-needle unit contains a single, pre-measured dose, the amount of medication, including narcotics, that is given a patient is readily ascertainable. Hence, accounting is facilitated and the proper charges to the patient can be made accurately and easily.

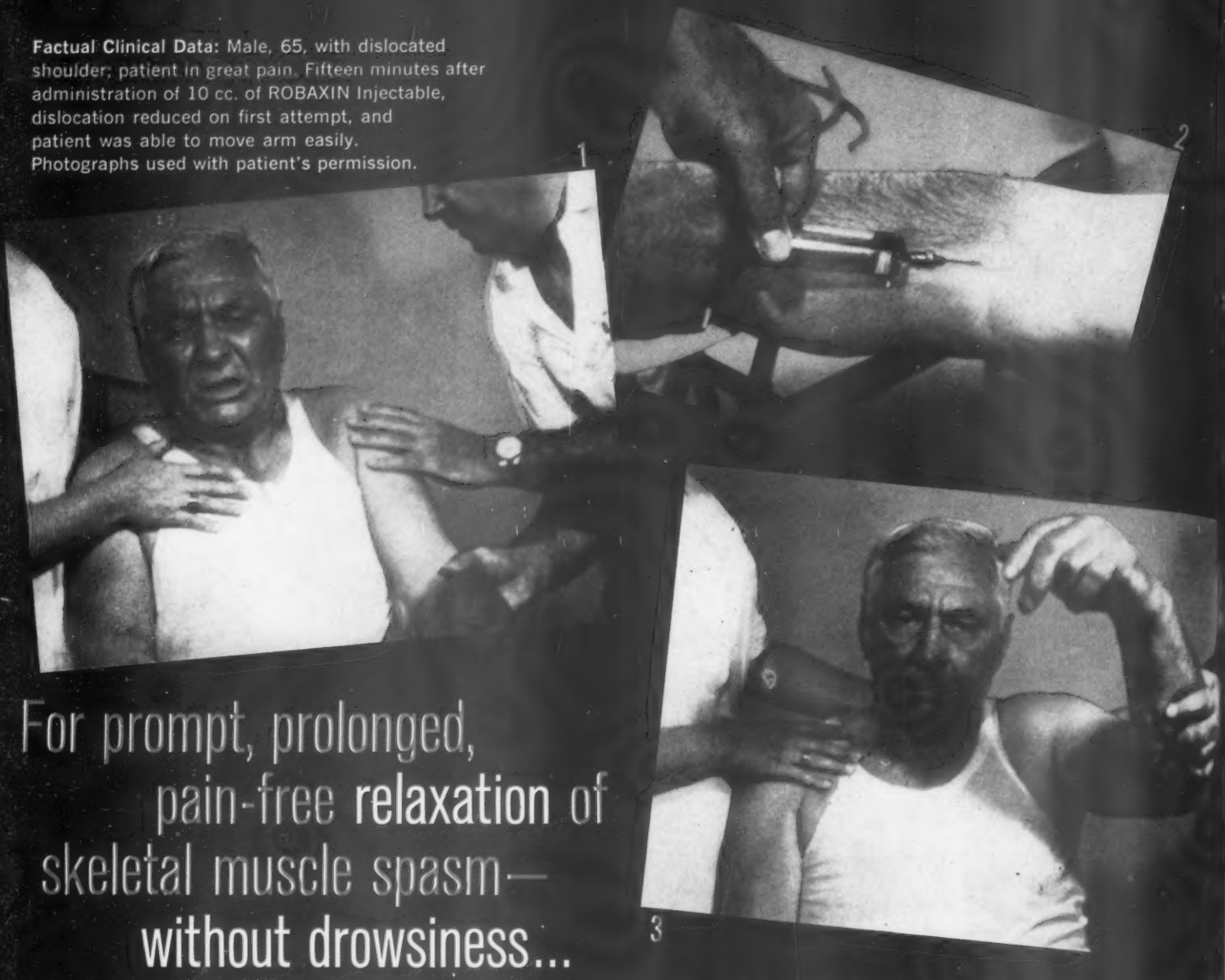
In summary

As you can see, adoption of the TUBEX system can have far-reaching effects. Efficiency and morale of the staff are improved. Labor costs—currently about 70 cents of every dollar spent by the hospital—are markedly reduced. Accounting, billing, and inventory control are made more accurate. The risk of malpractice suits is mitigated. The well-being of patients is enhanced.

The TUBEX system can presently supply more than 75 per cent of injectables commonly administered in hospitals. And medications not yet available in TUBEX form can be administered by means of empty, sterile cartridge-needle units. Thus, the TUBEX system is capable of meeting every need for injectables.

The TUBEX system is already in wide use. To learn more about the many benefits that the TUBEX system can bring to *your* hospital, please see your Wyeth Territory Manager or write to Wyeth Laboratories, P.O. Box 8299, Philadelphia 1, Pa.

Factual Clinical Data: Male, 65, with dislocated shoulder; patient in great pain. Fifteen minutes after administration of 10 cc. of ROBAXIN Injectable, dislocation reduced on first attempt, and patient was able to move arm easily. Photographs used with patient's permission.



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REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Grisolia, A., and Thomson, J. E. M.: Clin. Orthopaedics 13:299, 1959. 4. Hudgins, A. P.: Clin. Med. 6:2321, 1959. 5. Lewis, W. B.: California Med. 90:26, 1959. 6. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 7. Park, H. W.: J.A.M.A. 167:168, 1958. 8. Plumb, C. S.: Journal-Lancet 78:531, 1958. 9. Poppen, J. L., and Flanagan, M. E.: J.A.M.A. 171:298, 1959. 10. Schaubel, H. J.: Orthopedics 1:274, 1959.

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*Ayd, F. J., Jr.: New England J. Med. *261*:172, 1959.

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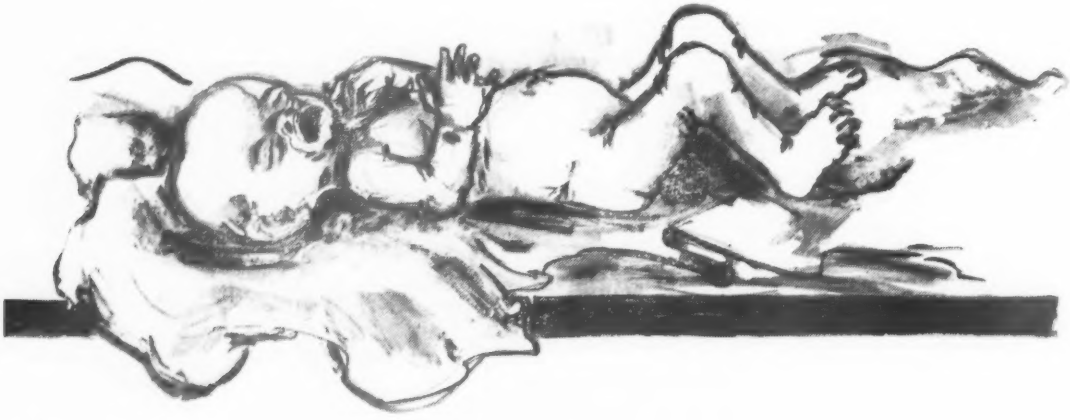

the situation: Four-month-old infant with staphylococcal pneumonia and empyema resistant to most antibiotics was allergic to antibiotic chosen after sensitivity tests. Thoracentesis produced 30-40 cc. of creamy, purulent fluid. Organism was Staphylococcus aureus, coagulase positive.

then Furacin was instilled: 0.2% Solution was diluted equally with physiologic saline and 10 cc. of mixture instilled twice daily into pleural space, with suction catheter clamped off for 1 hour. Fluid almost immediately became thinner and less viscous. Twenty-four hours later infant was less irritable, voluntarily started taking food. Instillations stopped. FURADANTIN® Oral Suspension prescribed. Recovery uneventful.

1. Perkins, J. L.: Kansas State M. J. (to be published).

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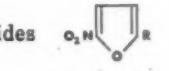

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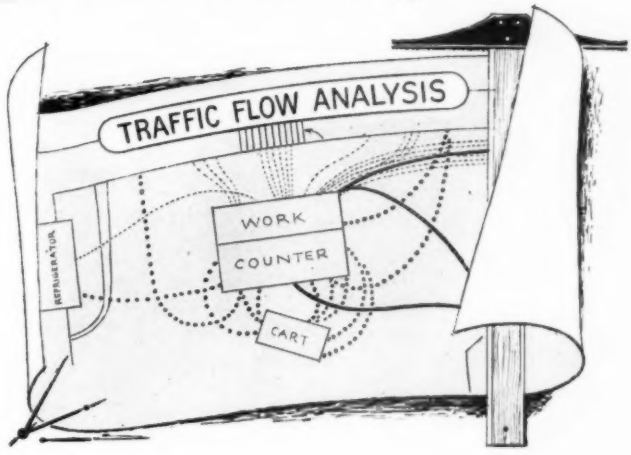
Modernizing the Hospital Pharmacy

The New Look that Saves Steps

by Alfred A. Mannino
EXECUTIVE DIRECTOR, HOSPITAL DEPT.
McKESSON & ROBBINS, INC.



In my recent trip around the country visiting hospital pharmacies, I found that along with the growing importance of the pharmacy operation has come a tremendous awareness of the need for modernization programs. Often, the increased demands upon hospital pharmacies simply could not be met profitably and efficiently without modernization. Over and over again, I was struck with the way in which scientific modernization had overcome what had previously seemed like insurmountable problems of size, space, and of course, money. It's one thing to plan a modern pharmacy for a new hospital and quite another to transform existing pharmacies into ones capable of meeting vastly increased responsibilities.

Perhaps the most outstanding example of modernization I saw is what has been done at a 1,000-bed midwestern hospital. You can well imagine what a challenge a hospital of that size presents for any pharmacy. The Hospital Administrator, Chief Pharmacist and the rest of the staff realized the need for modernization, but were faced with a real problem. The size and location of the pharmacy was fixed; there was no additional space available. What's more, the area involved was extremely inconvenient—a long, narrow space.

So there it was, a difficult modernization problem in a hospital so large few companies could handle it.

Knowing what you want from your hospital pharmacy is the first step in any modernization program, so the Administrator and Chief Pharmacist spent many hours defining the end result they wanted. Then McKesson took over. One of our design consultants studied the traffic flow in the pharmacy and made a detailed traffic flow chart of the pharmacy operation. Only with this blueprint of existing conditions could the design consultant have the basis for scientific modernization.

The next step was a thorough analysis of the proposed pharmacy operation, based on McKesson's Functional Check List for Planning Hospital Pharmacies. The following brief outline of the Check List should give you some idea of the many details the design consultant must bear in mind.

A. General Considerations
1) What services are to be provided?
2) Will the hospital pharmacy manufacture?
3) Number of staff expected to operate these facilities?

B. Location
1) Which departments and clinics receive the bulk of pharmaceutical service?
2) Will the pharmacy be centrally located to in-patient and out-patient services?
3) What method of distribution is to be used for medications?
4) Will bulk pharmacy stores be convenient to the pharmacy?

C. Functional Arrangement
1) What is the functional flow within the department?
2) What is the functional arrangement of various units?
3) What general storage facilities should be provided?
4) What major equipment is needed?

Finally, the modernization plan emerged, and I wish you could see the result—a modern, highly efficient pharmacy, scientifically planned so that production has been raised tremendously. The traffic flow saves steps, time and money. As much as a mile of walking is saved for every 125 prescriptions. And the amazing thing is that it has all been done in the same space as before!

Are you planning a new pharmacy? Modernizing an existing one? Whether your hospital pharmacy is large or small, take advantage of the specialized knowledge and experience of the McKesson Design Consultant near you. He will be glad to prepare a Traffic Flow Analysis of your pharmacy. This service is completely free and available to all hospitals within the area McKesson serves. Write me for the name of your nearby McKesson Hospital Service Department. Address: A. A. Mannino, McKesson & Robbins, 155 East 44th St., New York, N. Y.

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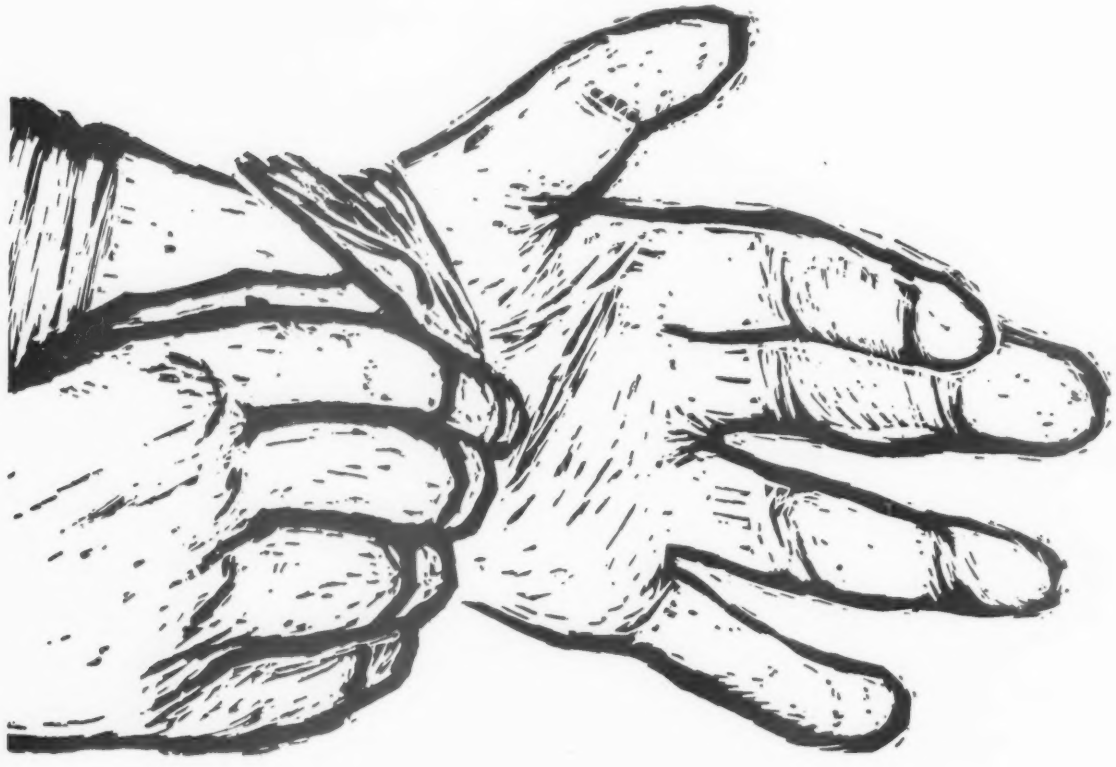
*Lamphier, T.A.: Paper accepted for publication in The American Surgeon.



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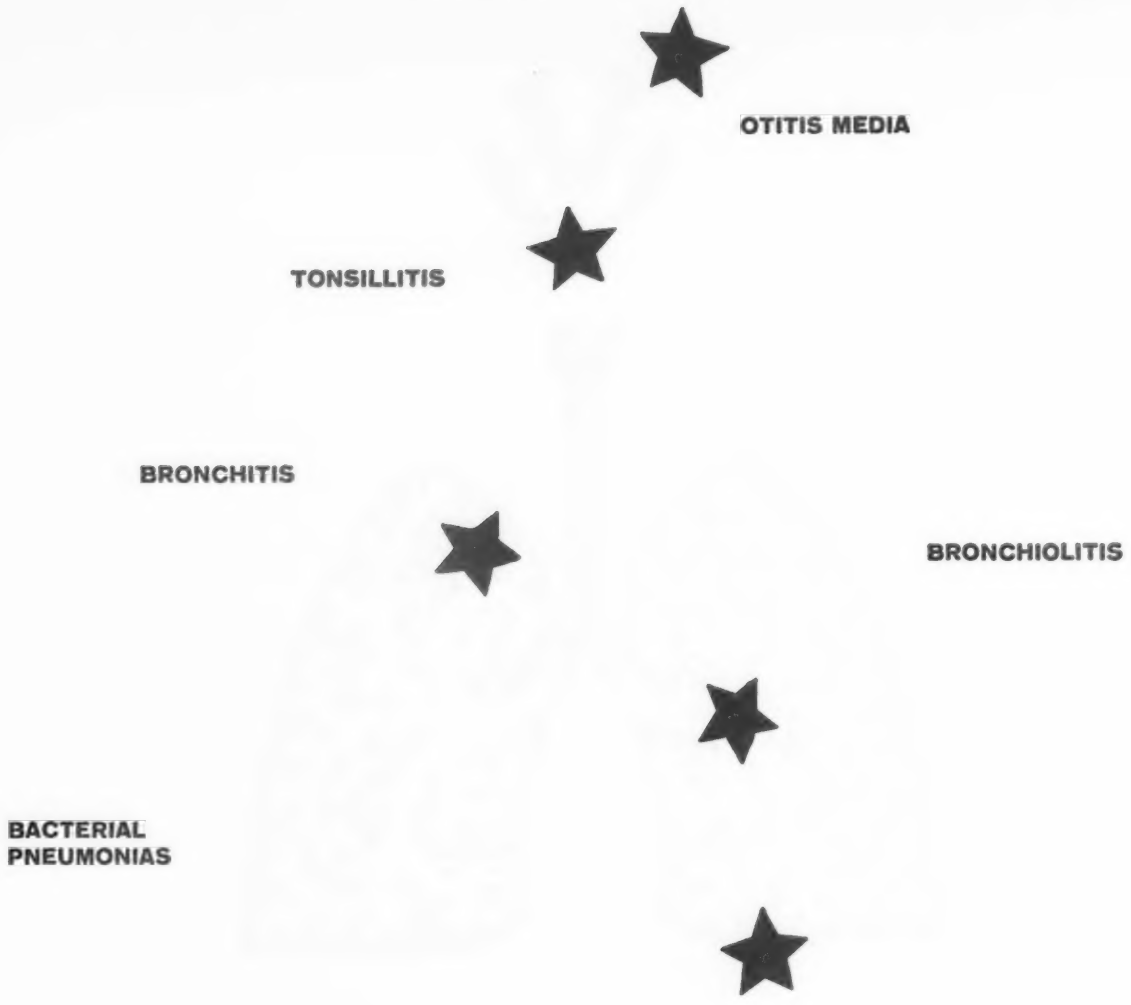

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1. Lysaught, J. N., and Cleaver, W.: Proceedings of the Detroit Symposium on Antibacterial Therapy (Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959).

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1. Romansky, M. J.. Ristocetin, Antibiotics Monographs, No. 12. New York, Medical Encyclopedia Inc., 1959.

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DEAR MEMBERS:

During the past year the Society has mourned the loss of two honorary members who were great leaders in the development and progress of Hospital Pharmacy.

Dean Edward Spease and Mr. H.A.K. Whitney symbolize the advancement in our field because they fostered better standards of practice through education and training.

The Executive Committee has agreed that the establishment of the Whitney-Spease Scholarship Fund of the ASHP will be an appropriate memorial by providing assistance to chosen graduate students in Hospital Pharmacy.

This is an invitation to you to participate in perpetuation of the contributions of Edward Spease and Harvey Whitney by supporting graduate education through the Whitney-Spease Scholarship Fund of the ASHP.

Your contribution will be beneficial to you and to Hospital Pharmacy. Please use the attached form to send your contribution.

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Southern California Society

Mr. Wendell Hill of Orange County Hospital has been elected President of the Southern California Society of Hospital Pharmacists. Other officers whose election was announced at the November 11 meeting are *Vice-President*, Mr. Chester Bazil, Veterans Administration Center; *Secretary*, Mrs. Jean Warner Jarvis, Long Beach Community Hospital; and *Treasurer*, Kikuyo Munemori, St. Vincent's Hospital. These new officers will be installed at the annual dinner meeting in January.

Florida Society

The Florida Society of Hospital Pharmacists held its annual meeting at the Hotel Robert Meyer in Jacksonville on December 3 and 4. The meeting was held in conjunction with the convention of the Florida Hospital Association.

A highlight of the seminar-type program was an address by Mr. Vernon Trygstad, President of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The title of Mr. Trygstad's presentation was "Target for Tomorrow." Other speakers included Mr. Burns Geiger, Manager of Pharmacy Service, Pfizer Laboratories; Mr. W. E. Arnold, Executive Director of St. Luke's Hospital; Mr. Emmett R. Johnson, Assistant Administrator of the Baptist Memorial Hospital; and Dr. Warren E. McConnell, Director of Pharmacy Services, Teaching Hospital of the University of Florida.

A panel discussion followed the presentation of papers, the speakers serving as panelists.

Mr. Weldon R. Rehburg, Mound Park Hospital, was installed as President for the coming year. In his address, President Rehburg called for increasing activity in obtaining active members, and outlined a plan for establishing "Area Chapters" in an effort to stimulate interest in the Florida Society.

Illinois Society

The December 8 meeting of the Executive Committee of the Illinois Society of Hospital Pharmacists was held at the Michael Reese Hospital.

The first order of business was a discussion on the sponsorship of the Society Newsletter. It was decided that the expenses of publishing and mailing the Newsletter be paid from the Society funds.

Mr. Edward Hartshorn gave a report on the plans for the annual Seminar. The Seminar will be held at the University of Illinois on March 22, and will be an all-day program. There will be a $2.00 registration fee for members of the Society.

The Illinois Society has accepted an invitation of the Chicago Branch of the American Pharmaceutical Association to plan and conduct the April meeting of the Association. It was decided to plan the Student Visitation Program to coincide with this meeting date, and to invite an outsider speaker for the program.

Greater Kansas City Society

The regular monthly meeting of the Society of Hospital Pharmacists of Greater Kansas City was held on December 8 at the Blue Cross - Blue Shield Building.

Plans for the program of the Pharmacy Section of the Midwest Hospital Association Convention were discussed. The convention will be held April 26-29, and a program, including topics on hospital administration and other departments in the hospital, as well as pharmacy subjects, has been planned.

The question of eligibility of pharmacists in osteopathic hospitals for membership in the Society was introduced for consideration. It was pointed out that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS makes no distinction in the type of hospital that employs the pharmacist, only that he be a registered pharmacist.

St. Louis Society

The December meeting of the Hospital Pharmacists' Association of Greater St. Louis was held at the Jewish Hospital in St. Louis. Mr. Don Wolff, a student at the St. Louis College of Pharmacy, was a guest at this meeting.

Mr. Robert Newton announced that copies of the State of Washington Hospital Pharmacy Law are being prepared for distribution to the members. These laws will be discussed at future meetings as a basis for proposing a Hospital Pharmacy Law to the Missouri Board of Pharmacy.

Following the meeting, an interesting film on the Indianapolis 500 Race was shown by Eli Lilly and Company.

New Jersey Society

The New Jersey Society of Hospital Pharmacists met at the Kuebler House at the Rutgers College of Pharmacy on December 3.

The meeting was devoted to the discussion and formulation of recommendations for changes in the Pharmacy Act which would be submitted to the State Board of Pharmacy. The discussion included a history of the legislation concerned with hospital pharmacies. The Society has prepared a draft of a bill to present to the State Board, but it was felt that the proposal needed more study. Before submitting any definite recommendations, the Society wishes to make sure they do not conflict with any provisions in the State Hospital Act or regulations of the Board of Health.

Akron Area Society

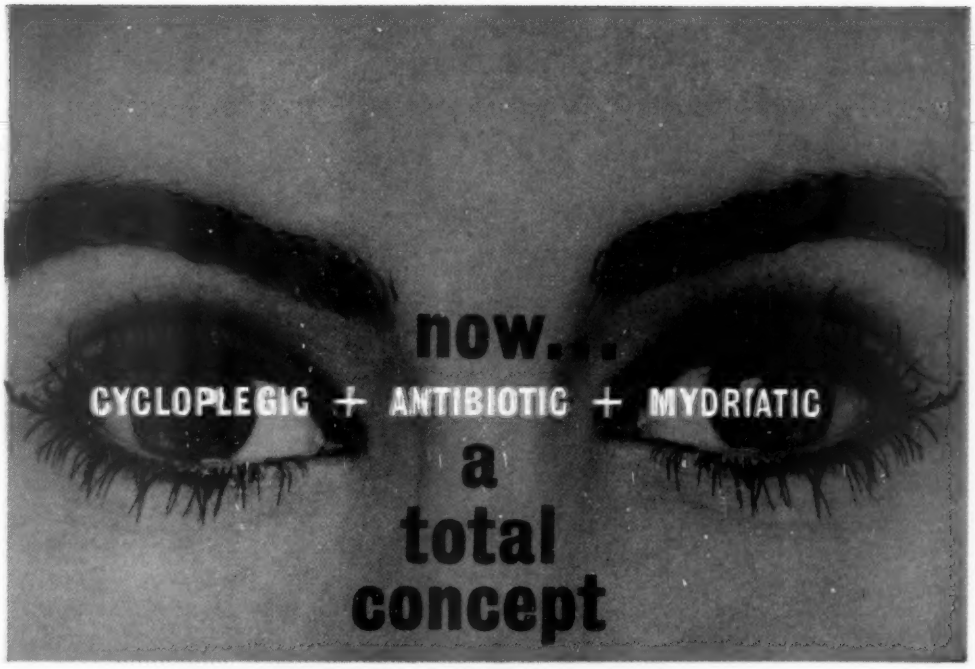
The Akron Area Society of Hospital Pharmacists met for its regular meeting on December 8 at the Alliance City Hospital. Mr. Paul Dickerson, President, presided at the meeting.

Plans for the Student Project were outlined in a report from the Project Committee. Tentative dates for the tour have been arranged for April or May, and await confirmation by the Deans of the respective Colleges of Pharmacy.

Other reports included those from the Membership Committee, and the Constitution Committee. A discussion on the recommended amendments to the Constitution and By Laws followed the report.

Michigan Society

The Michigan Society of Hospital Pharmacists met for its regular meeting on December 17 at the Veteran's Memorial Building in Detroit.



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References: 1. Miles, P. W.: Missouri Med. *56*:1243, 1959. 2. Sorsby, A.: Ann. Roy. Coll. Surgeons of England *22*:107, 1958. 3. Costner, A. N.: South. M. J. *48*:1192, 1955. 4. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34, 1955.

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References: 1. Miles, P. W.: Missouri Med. *56*:1243, 1959. 2. Costner, A. N.: South. M. J. *48*:1192, 1955. 3. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34, 1955. 4. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. *38*:831, 1954.

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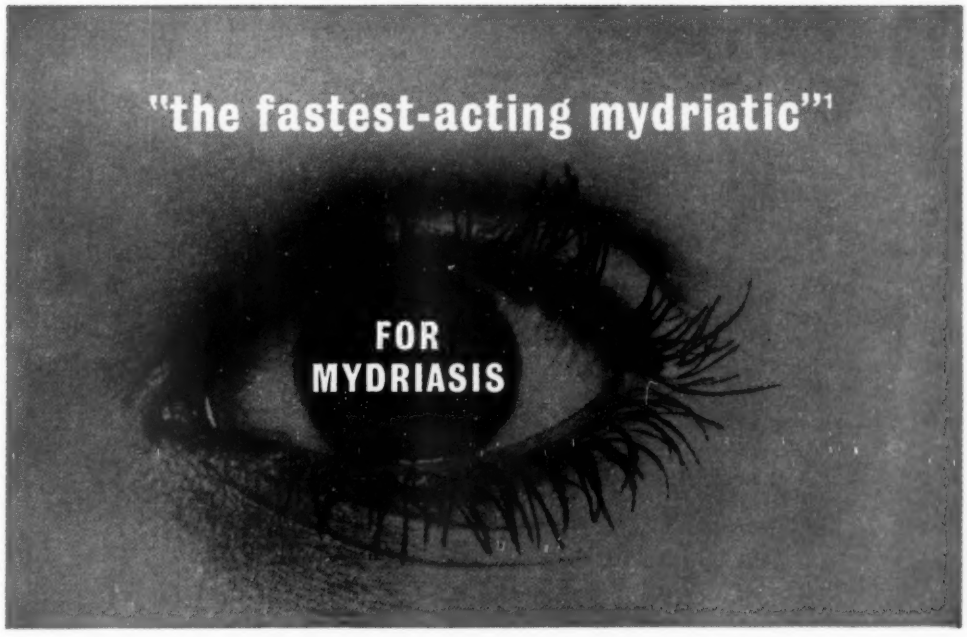

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References: 1. Miles, P. W.: Missouri Med. *56*:1243, 1959. 2. Priestly, B. S.; Medine, M. M., and Phillips, C. C.: to be published. 3. Costner, A. N.: South. M. J. *48*:1192, 1955. 4. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34, 1955. 5. New and Nonofficial Drugs: J. B. Lippincott Company, 1958, p. 243.

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Mr. Paul A. Freeman, Manager of Professional Relations for E. R. Squibb and Sons was the guest speaker. Mr. Freeman spoke on the subject "New Weapons Against Disease." He discussed the newer approaches to therapy using the corticosteroids, the more recent advances in diuretics, and the newer developments in the fight against neoplastic diseases.

Northeastern New York Society

On December 1 the Executive Committee of the Northeastern New York Society of Hospital Pharmacists met at the Albany Hospital. The purpose of the meeting was to consider the proposed Constitution of the New York State Council of Hospital Pharmacists. The proposed set of definitions requested by the State Board were also discussed.

On Saturday, December 19, the Northeastern New York society held its Second Annual Children's Christmas Party.

The guests were children of the members of the Society. The wives of members assisted in preparations for the party which was held at the Albany Hospital. Dr. Edward Bronsky of the Albany Hospital staff played the part of Santa Claus, and entertainment was provided by the Albany Boys Club Glee Club, under the direction of Mr. Louis Jeffrey, a member of the Society.

Virginia Society

The Virginia Society of Hospital Pharmacists held its regular quarterly meeting on December 5 at the University of Virginia Hospital, in Charlottesville, Virginia.

The guest speakers for the meeting was Dr. William Parson, Professor of Internal Medicine at the University of Virginia. Dr. Parson spoke on the subject of "Obesity."

A panel, moderated by Mr. R. David Anderson, discussed "Safety Practices in Hospital Pharmacy." The panel members included Miss Alice Smith, Associate Director of Nurses at the University Hospital; Mr. John F. Harlan, Jr., Associate Director of the University Hospital; and Mr. Wallace Thacker, Chief Pharmacist at Virginia Baptist Hospital.

Secretaries of ASHP Affiliated Chapters are urged to send reports of meetings to the national secretary promptly. Since the AMERICAN JOURNAL OF HOSPITAL PHARMACY appears on a monthly basis, reports must be received within five days after the meeting in order to be included in the forthcoming issue. We urge you to send details of the activities of your chapter for publication in this column.

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References: W. J. Kolff, "Acute Renal Failure: Causes and Treatment," The Medical Clinics of North America, *30*:1052 (July 1955).
Peter Forsham, "Symposium on Adrenal Corticoid Therapy," Metabolism, 7:19 (Jan. 1958).

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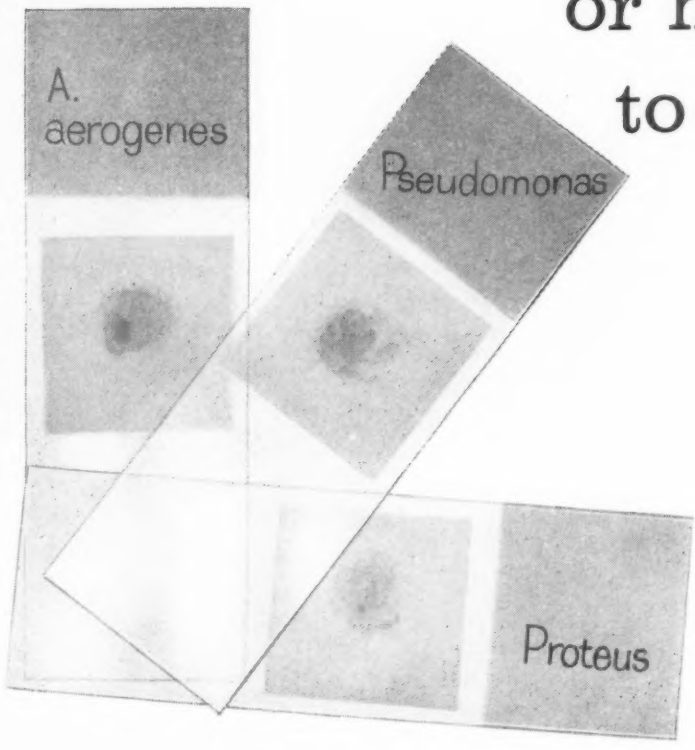

1. Department of Clinical Investigation, Lederle Laboratories, F. M. Phillips, Director. Interim Report on Clinical and Pharmacologic Investigations. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A.; Kunin, C. M., and Finland, M.: **München. med. Wchnschr.** To be published. 4. Roberts, M. S.; Seneca, H., and Lattimer, J. K.: Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 5. Vineyard, J. P.; Hogan, J., and Sanford, J. P.: **Ibid.**

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NEW MEMBERS

The following ASHP members sponsored the New Members listed in this issue of the JOURNAL. *The officers of the* SOCIETY *and the Committee on Membership and Organization appreciate the efforts of the individuals who have encouraged New Members to join the national organizations.*

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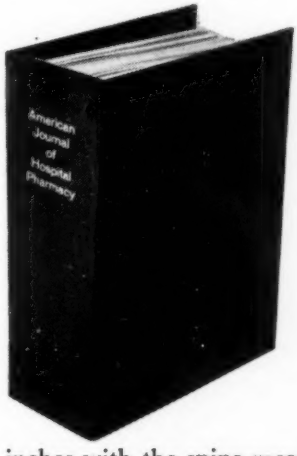

A loose-leaf binder for the AMERICAN JOURNAL OF HOSPITAL PHARMACY is now available from The Hamilton Press, Hamilton, Illinois. The new binder has been designed for THE JOURNAL and will hold the twelve issues satisfactorily. The binder is brown in color and "American Journal of Hospital Pharmacy" is embossed on it in gold. The binder is 9 by 12¼ inches with the spine measuring 4 inches.

The cost of the binder is four dollars ($4.00) each and orders may be directed to The Hamilton Press, Hamilton, Illinois.

A few copies of the loose-leaf binders for THE BULLETIN OF THE AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, which was published on a bi-monthly basis from 1946 through 1957, are available at two dollars ($2.00) each. On ordering binders, please indicate clearly whether you want binders for THE JOURNAL (twelve issues) or THE BULLETIN (six issues).

Lehn & Fink
PROFESSIONAL DIVISION

newsletter

FOURTH OF A SERIES WITH SIGNIFICANT SUGGESTIONS FOR CONTROLLING CROSS INFECTION

RECENTLY we've been flattered by the increasing number of requests for reprints of the earlier issues of STAPH NEWSLETTER. As noted above, this is the fourth of a continuing series. If you missed any of the earlier ones, or simply don't want to mutilate your journals by clipping them, we will be glad to send you copies. Just let us know which of the series you want or, if you like, write for the complete set.

Have you sent for your supply of our new instruction card on how-to-use Amphyl for disinfection of blankets, linens, and diapers? This is a handy 3" x 9" card planned for your use in teaching or discussion, and for posting on bulletin boards. As on the first six cards covering disinfection with Amphyl in other areas of the hospital, lively cartoon sketches make the short suggestions for use more interesting. Let us know how many cards you need and we will mail them right out to you. Please send requests to our new Toledo address shown below.

Although staph is still the insidious "star" of hospital infection, more and more reports of troubles from other pathogenic organisms are appearing, particularly Pseudomonas aeruginosa. For instance, the PHS-HEW Morbidity and Mortality Weekly Report cites an outbreak in a hospital nursery for premature infants.

"Six of 14 infants became ill during a 2-week period. One of the 6 developed meningitis and died; 1 baby had loose stools, 3 had eye infections and 1 a skin lesion. Laboratory reports on stools, eye discharges, and spinal fluid from the child who died were positive for Pseudomonas aeruginosa. Another episode occurred in the same nursery several weeks later when the only 2 infants on the ward at the time became ill. These babies had loose stools which were positive for Ps. aeruginosa. All infants who became ill had used a nebulizer, the others had not. Cultures from various apparatus in the isolettes were also positive for Ps. aeruginosa."

A significant report on 23 cases of pseudomonas septicemia in leukemia patients at the Clinical Center of the National Institute of Health is made by Dr. Claude E. Forkner, Jr. and his co-workers in the American Journal of Medicine (December, 1958, page 877). Twenty-two of the 23 were fatal. Median duration of life following the first positive blood culture was 4.0 days. Pseudomonas septicemia frequently occurred as a superinfection. Seventy-seven per cent occurred despite broad-spectrum antimicrobial therapy, whereas only 33 per cent of staph septicemias occurred under these same conditions.

Lehn & Fink synthetic phenolic disinfectants—Amphyl®, O-syl®, and Lysol® disinfectants, and Tergisyl® detergent-disinfectant are all highly efficient against Pseudomonas aeruginosa in the environment. Routine decontamination of floors, surfaces, blankets, and linens can be one of the most economic, effective, and simple control measures against superinfection. Here's why—it reduces the number of organisms available for spread by any route—contact, nasal, or airborne—in turn, reducing excess hospital days and thus reducing hospital operating costs.

"Staphylococcal pneumonia has become an increasing problem in children, particularly in infants under six months of age, in whom the largest number of cases occur, and in whom mortality rate is over 50 per cent. Thirteen deaths were recorded in the age group under 15, and all but one of these occurred before the age of six months." Harvey I. Meyers, M.D., and George Jacobson, M.D.: RADIOLOGY 72:665, May, 1959.

If you're planning on attending the AORN meeting in New York in February, you'll find lots of interest relating to control of staph infection. We understand that Dr. Ralph Adams' scientific exhibit on "How to Stamp Out Staph in the Operating Room" will be shown. In addition to hosting the exhibit, Dr. Adams will present a paper on the program elaborating on the closely integrated plan for infection control which is dramatized in the three-dimensional display. Only two infections occurred in 800 consecutive procedures at the Wolfeboro, New Hampshire, Huggins Hospital where Dr. Adams is Chief of Surgery.

The complete control system which has reduced the infection rate from 2% to .25% includes: cleaning and disinfecting all surfaces and areas vigorously with a combined detergent-disinfectant (Tergisyl®); linen and blanket disinfection with Amphyl®; strict control of what and who enters the O.R.; isolation of the patient's skin by impervious plastic skin drapes; proper attire and efficient masking.

Besides visiting Dr. Adams, we hope you will stop at the Lehn & Fink booth and visit with us. We'll look forward to seeing you.

How are your plans progressing for showing the motion picture, "Prevention and Control of Staphylococcal Disease," in your hospital? We've had so many requests for showings of this film produced by the Communicable Disease Center of the U.S. Public Health Service that we felt we had to make a few more copies available to our hospital friends. We like the pertinent, practical suggestions for overall control and think you will, too. If you'd like to plan a showing soon, please let us know. We will either mail it to you, or, if you prefer, arrange for our representative to assist you in setting up a meeting and helping to answer any specific questions you may have on the use of Lehn & Fink disinfectants to control infection.

As you know, samples of any or all of our products are yours for the asking. Try them. Also, our research laboratories and technical advisors are ready to assist you with any infection control problems. Please let me hear from you.

Charles F. Manz
General Sales Manager
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Dear Sirs:

Corrections

DEAR SIRS: On Page 607 of the AMERICAN JOURNAL OF HOSPITAL PHARMACY, there is a paragraph on the *Drug Topics Red Book*, 1960 edition.

We do appreciate the publicity on the 1960 edition of the *Drug Topics Red Book*. However, the cost of the *Drug Topics Red Book* is $9.00 rather than $2.00.

We wonder if a correction could be published in an early issue, simply stating that the cost of the 1960 edition of the *Drug Topics Red Book* is $9.00, not $2.00, as published on Page 607 of the November 1959 issue.

Thank you.

H. K. AMBROSE, *Vice President*

DRUG TOPICS RED BOOK
10 East 15th Street
New York 3, N. Y.

DEAR SIRS: I wish to call your attention to two apparent errors in the official list of membership by states on page 676 of the November issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY. Fred W. McEwen and E. L. Hammond are both listed under Missouri when they should be under Mississippi.

E. L. HAMMOND, *Dean*

School of Pharmacy
University of Mississippi
University, Mississippi

Reprints Requested

DEAR SIRS: We would appreciate very much having 100 reprints of the article entitled "Gaseous Sterilization of Pharmaceutical and Hospital Supplies" by Lewis C. Miner. This article appeared in the June (1959) issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY.

CARL W. BRUGH, PH.D.,
Research Bacteriologist

Wilmot Castle Company
Rochester, New York

Student Interest

DEAR SIRS: In the January (1959) issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY, there appeared an article by Charles J. Keller entitled "Practical Usage of Prescription Folder." If it is possible, I would appreciate receiving a reprint of this article. . . . I have thoroughly enjoyed reading back issues of your JOURNAL and have gained much knowledge from them.

FRANK E. RITCHIE, JR., *Student*

School of Pharmacy
The University of Connecticut
Storrs, Connecticut

DEAR SIRS: For use in the library, I should like to secure two copies of the "Proposed Safety Standards for Hospital Medication Procedures" which appeared in a recent issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY.

MRS. FRANCES EMLEY, *Librarain*

Program in Hospital Administration
The University of Michigan
Ann Arbor, Michigan

Interest in Formulary Service

DEAR SIRS: Enclosed is a check for which I would like to purchase a copy of the *American Hospital Formulary Service*. Please send all supplements issued.

Congratulations on a job so urgently needed in hospital pharmacy and so well done.

FRANCIS R. GIANNETTI, *Pharmacist*

P.O. Box 34794
Los Angeles 34, California

NOTE: The *American Hospital Formulary Service* is available at $15.00 per copy from The Hamilton Press, Hamilton, Illinois. To date the following three supplements have been issued:

Supplement 1: May 1959

Supplement 2: September 1959

Supplement 3: November 1959

A fourth supplement will be in the mail in February, 1960. Any subscriber to the Formulary Service who is not receiving supplements should write directly to The Hamilton Press, Hamilton, Illinois, giving the name and address *as entered for the original* Formulary.

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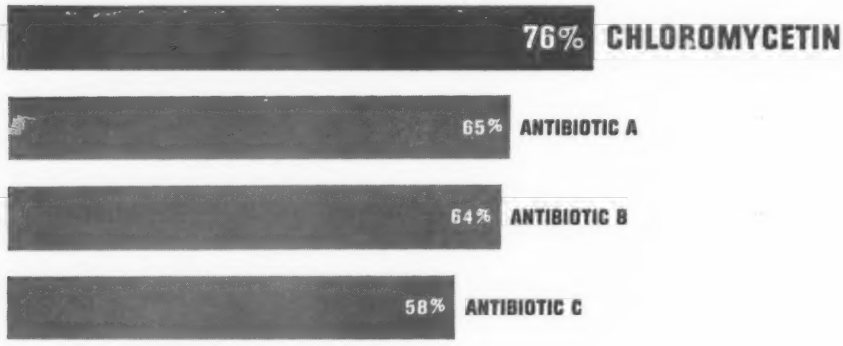

*Adapted from Leming, B. H., Jr., & Flanigan, C., Jr., in Welch, H., & Marti-Ibãnez, F.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 414.

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editorial

by DON E. FRANCKE

Physicians in Quandaries

► PHYSICIANS ARE IN A QUANDARY when really new drugs in their early stage of development are brought to the attention of the medical profession, according to Harry Beckman, M.D., Editor of *Year Book of Drug Therapy,* in his prefatory remarks to the newly issued 1959-1960 edition of the book. In his discussion of the problem, Dr. Beckman states that there is apprehension on the part of some physicians over the role and the methods of the pharmaceutical industry in the introduction of new drugs. Significantly, he indicates that a major reason for this apprehension is the medical profession's "sense of the failure of clinical teaching and practice to devise training technics in the evaluation and use of drugs."

There is a dissatisfaction among physicians, Dr. Beckman points out, with drug advertising. Condemned is the effort to break down sales resistance through the use of contrived illustration, gaudy and expensive colored releases, distorted bibliographic references and misrepresentation of the need and importance of the use of drugs in certain situations.

Apprehension is also expressed at the "side show atmosphere that increasingly characterizes some of the pharmaceutical house displays" at local and national meetings and at the methods used in detailing drugs by certain individuals of some pharmaceutical houses.

Dr. Beckman believes, however, the reason for the dissatisfaction lies much deeper than these considerations. He proposes that what certain members of the medical profession are really trying to express is their sense of the failure that exists in teaching physicians the technics of the evaluation and use of drugs. Physicians protest as a way of saying they feel helpless in this one aspect of their vocational activity, whereas in all others they feel adequate. In most situations the question of self interest in urging the use of specific methods does not arise. "But," according to Dr. Beckman, "when the new drug therapies are brought to our attention—the really new ones before there is anything in the easily accessible literature that directly applies, and before the American Medical Association Council on Drugs has published its judgement—in this situation we are in a quandary."

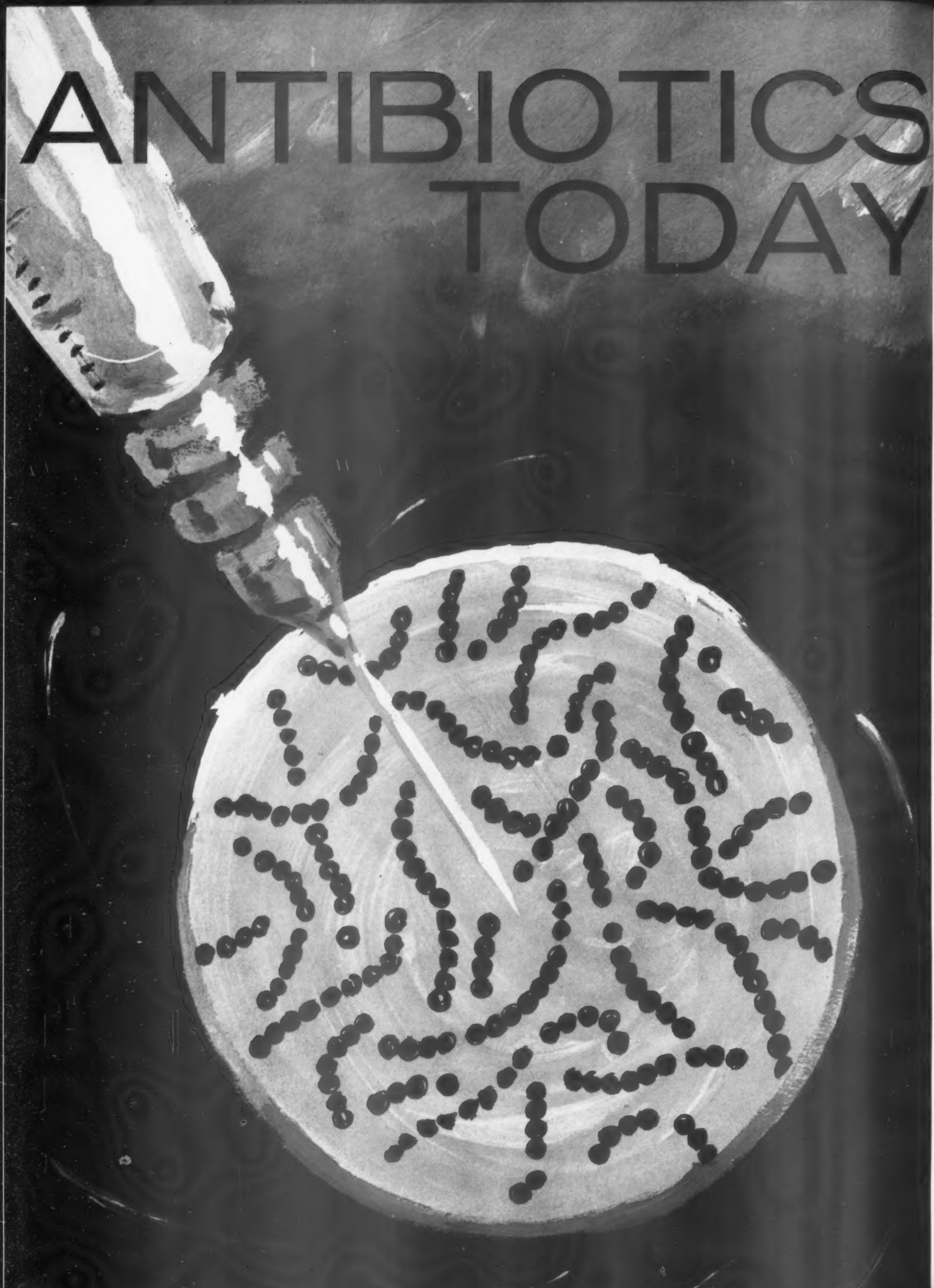
This quandary is attributable to attempts made to influence the physician to use a new drug before he has available an unbiased source of information as to its merits but, rather, is influenced by persons who will profit directly from his decision. This, Dr. Beckman states, is what physicians do not like.

After mentioning several possible solutions to the problem, some of which he immediately dismisses as inadvisable, Dr. Beckman singles out the desirability of encouraging individual physicians, by studying alone, to acquire the ability to form satisfying judgements on the merits of new drugs. To this end he has included two new sections in the current *Year Book of Drug Therapy.* One of these is a discussion of the "Bases for Judgement of a New Drug" which gives the physician the tests to which he may subject a drug before personally prescribing it for his patients. The second section is devoted to "The Year's New Drugs" and provides a list of most of the prescription items introduced in the twelve months preceding press time of the book, with expressions of personal opinion regarding the drugs in instances where it has seemed to be helpful.

All of this recalls to mind efforts of the ASHP to encourage rational drug therapy through the cooperative efforts of the Pharmacy and Therapeutics Committee and the medical staff in hospitals. Certainly the problem is more difficult and more complex than it has ever been—due to the greater number and complexity of the new therapeutic agents. But many hospitals now have the means for taking great strides in fostering a more careful evaluation of drugs—through their Pharmacy and Therapeutics Committees. One may hope that Dr. Beckman's "Bases for the Judgement of a New Drug" and the other helpful material in the new *Year Book of Drug Therapy* will be carefully read by physicians and pharmacists who are members of Pharmacy and Therapeutics Committees and that plans for a more dynamic program of rational drug therapy in the nation's hospitals may be sparked.

Year Book of Drug Therapy 1959-1960 Series is published by Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, Ill. 570 plus 80 pages. Price $8.50.

ANTIBIOTICS TODAY



a summary of recent developments in antibiotics reported at the recent symposium on antibiotics held in Washington, D.C.

► SEVERAL NEW ANTIBIOTICS and additional uses for established agents were reported at the Seventh Annual Symposium on Antibiotics held in Washington, D. C. in December.

Chairman of the Symposium was Dr. Henry Welch of the Food and Drug Administration who reported participation of representatives of more than 20 countries who contributed about 150 papers.

Among the new antibiotics reported were colistin, aspartocin, fervenulin, streptozotocin and rifomycin. New uses were described for paramomycin in amebic dysentery, amphotericin in systemic fungal infections, and griseofulvin for wider application in dermatology. Two new antitumor agents, streptonigrin and diazomycin, were added to swell the list already containing actinobolin, streptovitacin and the nonantibiotic agent cyclophosphamide, among others.

Significant papers reporting experiences with demethylchlortetracycline and pyrrolidinomethyl tetracycline were presented as were others discussing new developments in the synthetic penicillins.

Synthetic Penicillins

Commenting on the latter, Dr. Welch stated, "It is my personal opinion that one of the outstanding contributions this year is covered in the reports on the new synthetic penicillins, particularly from the standpoint of their possibilities for the future. To John C. Sheehan in this country, who first synthesized penicillin V and who first converted penicillin G to 6-aminopenicillanic acid and to the English workers, Doyle and Rolinson, who uncovered an economic source of this compound in fermentation broths, goes the credit for this unique and important development. It is apparent now that modification of the side chain attached to penicillanic acid may materially affect its antibacterial activity.

"The cue to this phenomenon is apparent in retrospect from the activity of synnematin, a penicillin with alpha aminoadipic acid as the side chain, described years ago and found quite active against gram-negative organisms, in contrast to the widely used penicillin G, with a benzyl substituent group, active mainly against gram-positive organisms.

"Innumerable synthetic penicillins, of course, are possible. In this country over 500 have already been prepared by the Bristol Laboratories. Perhaps here we have a key that in the near future may 'open the door' to a broad spectrum penicillin, to antifungal penicillins, antiviral penicillins or even to penicillins active against tumor cells by the correct manipulation of the guiding side chain. Since a great many compounds are possible, it becomes a question of guiding development of them in the proper direction. Already preliminary evidence is available concerning the kind of side chain or direction one must pursue to obtain increased stability and greater absorption. Here too, in retrospect, a lead was given by nature through the stable, rapidly absorbed phenoxymethyl (penicillin V). The new alpha phenoxyethyl penicillin, from the data to be presented here, is far better absorbed by man than is penicillin G. Futhermore, it is better absorbed than penicillin V, from which it differs only by one additional methyl (CH_3) group. It is of interest that the ***addition*** of a CH_3 group to penicillin V increased its ability to be absorbed by man while the ***deletion*** of a similar group from chlortetracycline accomplished a similar improvement in absorbability."

Historical Challenges

"The best remedy against the dangers of a mythology of science is for scientists not only to remember that some of the greatest problems of medicine are still unsolved after some 6,000 years of written history, but also to maintain a ***human*** and therefore antimythological attitude, for without it there can be no true progress of science," Dr. Felix Marti-Ibanez, Professor and Director of the Department of the History of Medicine, New York Medical College, told approximately 1,000 scientists at the opening of the Symposium.

"All throughout the history of medicine," Dr. Marti-Ibanez said, "the physician has been faced with great challenges that he has resolved by his genius and courage. The seven great historical challenges to medicine have been how to achieve survival in the 'desert-and-river' civilizations of Mesopotamia and Egypt; the philosophical inquiry into the nature of the universe, man and disease in classic Greece; the dreadful medieval pandemics; the exploration of the human body in the Renaissance; the investigation of human physiology in the Boroque period; the challenge of therapies early in this century; and the understanding of the nature and biochemical substrata of disease in our time.

"We have progressed from the anatomic notion of disease to the physiologic, and now to the biochemical. There are several constellations of basic challenges confronting Medicine in our time, which Medicine is now answering in seven directions: biochemical strengthening of the organic fortress, medical use of ecology, erradication of the basic agents of disease, synthesis of new drugs to combat 'old' diseases, synthesis of new drugs to combat 'new' diseases, new diagnostic techniques, use in research of new chemical agents.

"There is a danger of creating a mythology of science that, like Greek mythology, overestimates the power of the hero (the investigator), his weapons (technology), and his partial exploits (temporary, instead of final, results). The true guarantee of the future of medicine lies in the virtues of the men who are facing today the great challenges. The seven virtues of the great investigator (goodness, greatness, genius, spirit of inquiry, lucidity, patriotism, universality) are the real key to the future of medicine and the health and happiness of mankind."

Dr René J. Dubos suggested new lines of thought and research to develop drugs effective against surface infections. He pointed out that, "the universal practice is to look for substances active against pathogens at *p*H 7.0-*p*H 7.4 in simple culture media free of inhibitors." He suggested that, "these conditions favor the discovery of agents active in the blood stream, but they almost prevent the discovery of agents capable of acting in inflammatory and necrotic areas." Continuing, he stated, "I wonder whether the time has not come to broaden the range of the conditions used in screening tests both *in vitro* and *in vivo*. It might save investigators the boredom of rediscovering endlessly and uselessly substances identical or similar to those that other toilers in the same field have discovered before them under exactly the same conditions." Dr. Dubos pleaded for more research into the role host factors play in inhibiting or enhancing antimicrobial drugs.

"The challenge of new drugs to the pharmaceutical industry is not one but several," stated Dr. Austin Smith, President of the Pharmaceutical Manufacturers Association. "There are yet to explore new areas of disease not under control, there are areas of disease now partly under control but in need of refined techniques of therapy, there is a need for basic research development, there is need for new educational techniques, there is need for a better utilization of and increase in scientific man power, there is need for more clearly defining the drug industry's role in the medical care picture, and there is need for areas of friendly understanding if the benefits now available are to be most effectively utilized. The drug industry no longer can be considered as simply a supplier of pills and powders; its role in the welfare of mankind is confronting it with new challenges and broadening areas of responsibility. The industry will have to cope with these challenges and responsibilities but, in addition, the other members of the community will have to recognize how industry and they voluntarily can together do a better job than can each alone, particularly if an element of government compulsion is involved."

"The challenge of the Food and Drug Administration to continue to provide a high caliber of review for new drugs, is one we'll gladly meet as we have in the past," said Dr. William H. Kessenich, its Medical Director. "In the case of drugs as in no other commodity, the motivating consideration must be the welfare and benefit of the public and not just the common lure of the market place."

Discussing the challenge of new drugs to the practicing physician, Dr. John J. Curry, Associate Clinical Professor of Medicine at Georgetown University, pointed out that "as more potent and potentially more toxic drugs are introduced together with the improvement in diagnosis and medical practice that they will bring about, the problem of disseminating this knowledge to our practicing physicians becomes more acute. The various specialty groups and more recently the Academy of General Practice have encouraged post graduate studies. There is need for much greater effort. A 'Flexner type' survey of post graduate study needs should be undertaken preferably under the auspices of the American Medical Association . . ."

"Study courses should be set up utilizing teams of clinicians and research workers from the universities and the drug industry under the direction of local county and state medical societies. In this way the needs of local physicians can be best interpreted. If necessary attendance at these courses should be compulsory. These courses should be open to bonafide medical science writers and drug detailmen," Dr. Curry stated.

Dr. Curry suggested, "Yearly reviews of basic drugs should be published under the auspices of the American Medical Association Council on Drugs. It is not sufficient to determine only that a drug is safe and has some effectiveness." Continuing, he said, "The present day method of bulk advertising and innumerable drug magazines and pamphlets has collapsed from sheer weight."

► ACTINOBOLIN has been shown to be active against transplanted mouse tumors and leukemias. It also appeared to have some antileukemic activity in patients with acute leukemia. Intravenous administration of the drug, however, produced undesirable side effects such as nausea, vomiting and severe hypotention. Because oral administration possibly might result in attenuation of these side effects without loss of antitumor activity, comparative studies of blood levels, tissue levels and urinary excretion after parenteral and oral administration were undertaken. Experiments were done in mice, rats and man. Concentrations of drug were determined by microbiologic assay with *Sarcina lutea* as a test organism.

Rats and mice which had received single doses of 1500 mg./Kg. of actinobolin excreted in the urine 50-70 percent of the dose after intravenous injection, but not more than 10 percent after oral administration. No increase of gastrointestinal absorption in rats could be achieved by adding glucosamine, by using peanut oil or propylene glycol as a vehicle, or by changing the *p*H of the actinobolin solution. In all tissues, except brain, actinobolin could be detected.

One patient was given a dose of 100 mg./Kg. (total 1360 mg.) by intravenous infusion over a period of four hours.

During this period, a serum level of 60 ug./ml. was found. Four hours after termination of the infusion, no actinobolin (20 ug./ml.) could be detected. Urine specimens were collected during the infusion and for several hours thereafter. Actinobolin was detected one hour after initiation of infusion and reached a peak concentration in four hours. Twenty-four hours after termination of the infusion, low concentrations could still be detected in the urine. After oral administration urinary excretion was delayed slightly and was considerably less than after intravenous injection. Oral administration of high doses caused diarrhea. It would appear that, since the absorption of actinobolin from the gastrointestinal tract is very low, and since the amount to be given is limited by diarrhea, it is unlikely that therapeutic effects will be obtained by oral administration. These studies were reported by Cappuccino and Oettgen of the Sloan-Kettering Institute for Cancer Research, Memorial and James Ewing Hospitals and Cornell University Medical College, New York.

► AMPHOTERICIN B produces certain undesirable and occasionally grave side effects following drip infusion by which it currently is administered to patients with deep mycotic infections. Oral administration is reported to be ineffective according to Campbell and Hill of Walter Reed Army Institute of Research, Washington, D. C.

The survival time of mice with experimental coccidioidomycosis, histoplasmosis and cryptococcosis, however, was extended indefinitely in a series of prolonged experiments in which such animals were treated with an infusion preparation of the drug (Lot 4374) added to their drinking water in appropriate concentrations. This oral means of administration was effective in both delayed and immediate therapy regimens, and produced no apparent side effects in the highest dosages employed (approximately four times that tolerated by humans). At no time was the drug demonstrable in sera. Results indicated that further trial with oral administration of this form of the drug in human mycotic infections is warranted.

Clinical experiences with amphotericin B were reported by Baum and Schwarz of VA Hospital, University of Cincinnati, College of Medicine and the Jewish Hospital, Cincinnati. Thirteen cases of deep fungus diseases have been treated at four hospitals in Cincinnati since December, 1956. These have included 6 cases of histoplasmosis, 5 of North American blastomycosis and 2 cases of cryptococcosis. Follow-up ranges from one month to two and one third years. Results reveal that 4 of the cases of histoplasmosis were acute diffuse pulmonary lesions and all are well three to eighteen months after treatment. One of the 2 cases of cavitary histoplasmosis died of coexisting lung cancer while the other case is well.

Four of the 5 cases of blastomycosis had skin and pulmonary active lesions, all cleared and remained well for the two to four months of follow-up available, after treatment. The fifth case presented was an isolated blastomycotic arthritis which cleared with therapy. No reactivation has been noted in three months. One case of cryptococcosis was exclusively pulmonary with complete clearing of lesions by x-ray maintained for six months. The other case is one of meningitis with clinical and cerebrospinal fluid clearing maintained for the one month follow-up. Almost all patients had chills, fever, anorexia, nausea, emesis, rising BUN together or separately. Only 1 patient was without side effects and he was a 2⅓ year old child.

Ten patients with American leishmaniasis (1 with the mucous form, 4 with the cutaneous form and 6 with the mucocutaneous form) were treated with amphotericin B at the Department of Dermatology, Minas Gerais Medical School, and at the "Instituto Nacional de Endemias Rurais," Research Center of Belo Horizonte, Brazil. Five patients (cases 3, 5, 6, 7 and 9) had been previously treated with antimonial and/or arsenical drugs, with no results, and the remaining patients had not received any treatment whatsoever.

Amphotericin A/B tablets were administered to 5 patients (cases 1, 3, 4, 5, and 6) with poor or no results, after total doses ranging from 36 Gm. to 240 Gm. Amphotericin B was administered to this group and to 5 additional patients, in intravenous drip, at a maximum daily dose of 50 mg. suspended in 500 ml. of aqueous 5 percent dextrose, over 3 to 4 hours. The total dose ranged from 200 mg. to 1,450 mg. No relapse was noted during follow-up periods ranging from 15 days to 10 months.

Results were excellent and complete healing of the cutaneous and mucous lesions was obtained in all cases. Good tolerance to the drug and absence of toxicity were evidenced by clinical observation of the patients and control laboratory studies (liver function test, urinalysis, blood count and electrocardiogram). Febrile reactions and slight venous irritation were the only side effects observed.

The present investigation allows the conclusion that amphotericin B is effective in the treatment of American leishmaniasis according to Furtado of the Minas Gerais University, Belo Horizonte, Brazil.

The effect of amphotericin B upon the respiration of three strains of *Cryptococcus neoformans* isolated from human sources was studied by the Warburg method. Washed organisms were suspended in M/15 phosphate buffer, *p*H 7.0, and manometric measurements were carried out at 37°C. Results of these observations indicate that amphotericin B exerts a profound depression on the oxidative glycolytic processes of *Cryptococcus neoformans*. These studies were reported by Rhoades and Muchmore, University of Oklahoma School of Medicine and the Veterans Administration Hospital, Oklahoma City.

The *in vitro* effectiveness of amphotericin B against *Leishmania brasiliensis* was evaluated at the Department of Microbiology of the School of Odontology, Minas Gerais University, and at the Research Center of the "Instituto Nacional de Endemias Rurais," in Belo Horizonte, Brazil by Futado and Cisalpino. *Leishmania brasiliensis* was shown to be susceptible to the drug up to a concentration of 0.01 ug./ml. of 2 percent aqueous dextrose and Rugai's modified medium. Other tests performed showed the high leishmanicidal action of amphotericin B at the above-mentioned concentration.

Trial of an amphotericin B - tetracycline combination was reported by Kozinn, Burchall, and Taschdjian of Maimonides Hospital Brooklyn, and Beth Israel Hospital, New York. The danger of candidiasis during and after broad spectrum antibiotic therapy makes it desirable to combine antibacterial with anticandidal medication. The report deals with the efficacy of a combination of tetracycline with the anticandidal antibiotic amphotericin B in 53 children, who were treated for tonsillitis, furunculosis, croup, otitis media, and upper respiratory tract infections of varying etiology. The daily dosage was 25 mg. of tetracycline and 5 mg. of amphotericin B per kilogram body weight and was given in four administrations in 24 hours. Each patient received in the course of therapy at least 60 ml. of the medication, a syrup containing per milliliter 5 mg. of amphotericin B and 25 mg. of tetracycline. Therapeutic effect of the medication was uniformly good, indicating that amphotericin B did not interfere with the action of tetracycline. No toxic or

allergic reactions were observed. Stool yeast counts, performed before and after therapy, showed a significant drop in the gastrointestinal yeast flora in the great majority of the patients. None of the patients developed clinical candidiasis. Miscibility of the medication was satisfactory, and the taste was acceptable to the patients.

► ASPARTOCIN is a new polypeptide antibiotic produced by *Streptomyces griseus* var. *spiralia* grown on a medium consisting of protopeptone, molasses, Edamine, magnesium sulfate, calcium carbonate and an antifoam agent. Aspartocin is precipitated from the fermentation mash by the addition of calcium chloride and further processing yields the crystalline calcium salt. Aspartocin has similarities to amphomycin, but is more active and can be readily differentiated from amphomycin by paper chromatography and paper electrophoresis. Chemical studies indicate that aspartocin consists of amino acids and a fatty acid fraction. Aspartic acid, glycine, L-proline and L-valine have been identified as components of aspartocin, according to Shay, Adam, Martin, Hausmann, Shu, and Bohonos of Lederle Laboratories.

Streptomyces griseus var. *spiralis* has a relatively low oxygen requirement, and phosphate ion markedly interferes with the synthesis of the antibiotic. The importance of preferential carbon and nitrogen sources, as well as other required nutrients was discussed by Darken, Jensen, and Shu of Lederle Laboratories.

Aspartocin is an antibacterial peptide with antagonistic properties essentially directed against gram-positive microorganisms. Under usual laboratory conditions the compound does not show exceptional *in vitro* activity, but changes in cultural environment can markedly alter the apparent activity of the drug. Omission of phosphate ions or the incorporation of calcium ions enhance *in vitro* activity in broth cultures. Antibacterial activity is somewhat antagonized by normal horse serum in trypticase soy broth, but is slightly potentiated in brain heart infusion broth. Sheep erythrocytes, suspended in physiological saline are not hemolyzed below a drug concentration of 500 mcg./ml. A preliminary investigation indicates that the antibiotic is bactericidal in its action. Staphylococci develop resistance to aspartocin at a slow rate and to a relatively low level. Streptococci, appearing more sensitive to the drug, develop a lesser degree of resistance. The compound is effective, *in vitro*, against bacteria made resistant to the tetracyclines, leucomycin, erythromycin, spiramycin, magnamycin and puromycin. It is as active against a variety of penicillin and tetracycline-resistant staphylococci and streptococci isolated from clinical sources as it is against sensitive representatives of these organisms, according to Kirsch, Dornbush, and Backus of Lederle Laboratories.

The subcutaneous and intraperitoneal potency of aspartocin relative to chlortetracycline was determined in three standardized infections in mice. Aspartocin was also evaluated intravenously against two strains of Staphylococcus by Redin and McCoy of Lederle Laboratories. On an intraperitoneal dosage basis, aspartocin was equal in activity to chlortetracycline against the Staphylococcus Smith infection, and 10 to 20 times more potent than chlortetracycline against the Streptococcus C203 and *Diplococcus pneumoniae* SVI infections. Relative to chlortetracycline, by subcutaneous injection, aspartocin was one-fifth as potent in the Staphylococcus infection, about equal in the Streptococcus C203 infection, and about 8 times as active in the Diplococcus infection. Aspartocin was equal to tetracycline on an intravenous dosage basis against Staphylococcus Smith, and was effective against a tetracycline-resistant strain of Staphylococcus. As tested, aspartocin was inactive against *Klebsiella pneumoniae* AD, *Pasteurella multocida* 310, and *Mycobacterium tuberculosis* H37Rv infections in mice. Aspartocin was inactive orally. Dose-effects curve parameters and relative activities were determined.

► COBALT POTENTIATION of various antibiotics combined with cobalt was reported by Naranjo and de Moreno of the Universidad Central y Laboratorios L.I.F.E. Quito, Ecuador. The study was performed in lots of 10 white mice of 20-22 grams weight. The following microorganisms were tested: *Micrococcus pyogenes* v. *aureus*, *Streptococcus pyogenes* (haemolytic), *Escherichia coli* and *Klebsiella sp.* A suspension of microorganisms in culture for 18 hours was injected into the animals by intraperitoneal route. The following was determined: (1) The amount in millions of bacteria necessary to kill 50% of the mice (LD_{50}) 24 hours after injection of the culture. (2) The average effective dose of penicillin needed to protect 50% of the animals (ED_{50}) when injected with four times the LD_{50} of each germ. (3) After different trials, using penicillin as control, the dose of 0.5 mg./Kg. of cobalt chloride was selected for combination with the antibiotics. (4) The ED_{50} of penicillin, oxytetracycline, Signamycin and colimycin necessary to protect the animals against four times the LD_{50} of each microorganism, was determined. In one series, the antibiotic alone was used and in the other series the antibiotic associated with cobalt. It was found that the cobalt was able to increase the activity of different antibiotics in varying degrees, depending on the antibiotic and organism involved.

► COLISTIN SULFATE and sodium colistinmethanesulfonate are two forms of a new antibiotic, colistin, obtained by Koyama and his associates in Japan from *Bacillus (aerobacillus) colistinus*. They have been studied and used for several years in Japan, Italy and France, and for the past year, in this country. Both possess marked bacteriostatic and bactericidal activity against most gram-negative bacteria and lesser activity against gram-positive bacteria and fungi. Most susceptible bacteria are killed or inhibited by 0.05 to 3.0 mcg.(base) of either substance per ml. With sensitive strains there is no appreciable reduction in their *in vitro* activity in the presence of serum. Against Proteus strains their *in vitro* activity is quite variable, but most strains are not sensitive to ordinarily obtainable blood concentrations. Both forms give excellent protection in mice infected with *E. coli* and *K. pneumoniae*. Resistant strains of sensitive organisms are produced with difficulty *in vitro* and most of the mutants isolated do not prove to be stable. Resistance incident to therapy has not been reported. Strains of bacteria can be resistant to one or several of the broad-spectrum antibiotics while remaining sensitive to colistin sulfate and sodium colistinmethanesulfonate. Chemically, these are basic polypeptides resembling the polymyxins. However, they differ chemically and pharmacologically from any known polypeptide antibiotic. Acute, subacute, and chronic toxicity studies in several species show that sodium colistinmethanesulfonate is appreciably less toxic than colistin sulfate. Pharmacodynamic studies also demonstrate definite differences between the two substances. After intramuscular administration of sodium colistinmethanesulfonate in man and experimental animals, high blood serum levels are obtained very rapidly. Single intramuscular therapeutic doses (1.0-2.0 mg./Kg.) give a high blood serum level within 30 minutes, with peak levels after 2 and

4 hours, and detectable levels for 12 to 24 hours. It is excreted fairly rapidly in the urine, as evidenced by high urine concentrations and total excretion over a 24-hour period. Neither form is appreciably absorbed from the gastrointestinal tract. Because of the effectiveness of colistin sulfate and sodium colistinmethanesulfonate against gram-negative bacteria, their favorable therapeutic index, and the comparatively low rate of associated microbial resistance, they should fill an important need in chemotherapy, according to Schwarts, Warren, Barkley, and Landis, Warner-Lambert Research Institute, Morris Plains, N. J.

In vitro susceptibility tests with 58 strains of bacteria showed that colistin inhibited the coli-aerogenes, Pseudomonas, Salmonella, and Shigella groups, according to a study made by Wright and Welch of the Food and Drug Administration, Washington, D. C. In all cases colistin was more active than polymyxin B. Colistin was relatively inactive against proteus, staphylococcus, and streptococcus strains. The toxicity of colistin sulfate and colistin sodium methanesulfonate was observed in mice and rats using intravenous, intramuscular, intraperitoneal, subcutaneous and/or oral routes of administration. Given intravenously in mice the methanesulfonate appeared to be much less toxic than the sulfate. In rats given sublethal intraperitoneal or intramuscular doses of either preparation kidney damage was minimal; an unusual finding was severe inflammation and ulceration of the stomach in rats receiving colistin sulfate. Orally there was no stomach irritation. Stomach lesions were not observed in mice. Blood concentrations and urinary excretion were determined following single and multiple intramuscular doses of colistin sodium methanesulfonate in man. A single 15 mg. dose gave an average peak serum concentration at 2 hours of 0.95 ug./ml., while a 150 mg. dose gave 7.6 ug./ml. About 39 percent of the dose was recovered in the urine in 8 hours. No colistin was detected in the blood after a single oral dose of 221 mg.; however, there was some activity in the urine.

Sodium colistin methanesulfonate was given by Blaustein of Booth Memorial Hospital, Flushing, New York, to 20 subjects. Groups of ten each received 75,000 units and 37,500,000 units in five days. Complete blood counts, liver and renal function tests were performed initially after three and six days. In summary, the injections were not found to be painful. No patient had any subjective or objective symptoms following therapy. No alterations of the blood count, liver or renal functions were noted. A second study consisted of a comparison of sodium colistin methanesulfonate with 17 other antibiotics in checking out 80 gram-negative organisms in disc sensitivities studies. Results indicated sodium colistin methanesulfonate to be ineffective in sensitivity studies against otherwise resistant Proteus strains. However, a high degree of sensitivity was demonstrated against resistant strains of *Pseudomonas pyocyaneous* and intermediates of the coli-aerogenes group. The drug was at least equally effective against *Escherichia coli, Escherichia freundii, Aerobacter aerogenes, Bacillus anitratum, Paracolobactrum aerogenes, Paracolobactrum coliforme* and *Paracolobactrum intermedium.* In some cases a high degree of sensitivity was noted in otherwise resistant varients of *Escherichia coli* and *Paracolobactrum coliforme.*

Eighteen strains of *Pseudomonas aeruginosa* recovered from the blood stream, urine and skin of 11 burned patients demonstrated excellent tube sensitivity at the bactericidal level (0.9-3.9 ug./ml.) to colistin sulfate. These same strains exhibited insensitivity to neomycin and kanamycin (25 ug./ml.) and were somewhat refractive to polymyxin B (5-20 ug./ml.). Thirteen other strains of *Ps. aeruginosa,* non-nosocomial in origin (feces, ear) tested by the tube method, also demonstrated great sensitivity to colistin sulfate (0.19-3.1 ug.) but were considerably more sensitive to neomycin and kanamycin (0.39-6.3 ug.). The polymyxin B sensitivity of these strains was greater than those obtained from burn patients. Acquisition of resistance to colistin sulfate was not enhanced in any of the 31 strains by as many as 10 sequential transfers through sub-cidal doses of this antibiotic. Because of the great sensitivity of these organisms to colistin sulfate and their apparent inability to develop resistance to this antibacterial agent, it is believed that colistin sulfate may prove to be a drug of great merit in the management of serious gram-negative bacterial infactions such as *Pseudomonas septicemia* which so frequently occurs in burned patients. This study was reported by Graber, Tumbusch, and Vogel, of the Brooke Army Medical Center, Fort Sam Houston, Texas.

Clinical and laboratory observations have been collected by McCabe and Jackson, University of Illinois College of Medicine, Chicago, upon patients with chronic urinary tract infections, septicemia, endocarditis or wound infections due to gram-negative bacteria and who were treated with colistin. All patients received 50 mg. by intramuscular injection every six hours. Antibacterial activity could be demonstrated in the serum and urine of these patients. Among patients with chronic urinary tract infections the clinical and bacteriologic results during and immediately following treatment were good. Observations three months after the completion of colistin therapy showed that a bacteriologic cure was obtained in more than 50 percent of patients followed for this period. All patients with pseudomonas wound infections had gratifying clinical and bacteriologic results. Only three of the seven patients with gram-negative septicemia were cured or significantly improved. Some degree of drug toxicity was exhibited by thirteen patients but it necessitated the discontinuation of treatment in only two. The most common reaction was paresthesias which were severe in two patients and led to the cessation of treatment in one. Leukopenia possibly related to the administration of colistin was observed in one patient but it did not recurr upon readministration of colistin.

Serum concentrations following various intramuscular doses have been studied by Boger and Gavin of Norristown State Hospital, Norristown, Pa., and also the fractional urinary recoveries. In a space of eight hours, approximately 60 percent of a given intramuscular dose is recovered in the urine. This urinary recovery appears to be intermediate between that of the tetracyclines and that of penicillin. Following the intramuscular administration of 30 and 100 mg. (one and three million unit) doses, the diffusion of colistin into the cerebrospinal fluid reflected the quantity of drug administered intramuscularly. The effect of probenecid on the renal excretion of colistin was investigated, and also the effects of age upon the renal excretion pattern. Certain inconstancies of dosage in the vials supplied for clinical investigation have been studied, and also certain vagaries of the antibiotic assay of colistin were discussed.

Colistin sulfate is poorly absorbed from the alimentary canal, a characteristic which with its antibacterial range, suggests a potential as an intestinal antiseptic. Colistin alone was employed orally in several dose schedules and in combination with propionyl erythromycin in a total of 21 hospitalized patients, divided among the various regimens. These studies were reported by Shidlovsky, Fetzer, and Prigot of Harlem Hospital, New York. Assays of stool indicated that a total of 400 mg. of colistin, given alone in 4 equal doses in one day, was capable of consistent numerical suppression

of the total gram-negative flora and, to a lesser degree, of staphylococci. When this dosage was given simultaneously with 2 Gm. of propionyl erythromycin there was numerical reduction in both the fecal streptococci and staphylococci, in addition to the total count and the gram-negative flora. No untoward reactions to either antibiotic occurred.

A study of the effectiveness of colistin sulfate by the oral route was carried out by Greengard and Aliseda of Cook County Children's Hospital, Chicago. This series consisted of 103 infants from birth to one year of age all with acute diarrhea. There were 54 infants in the colistin sulfate treated group and 49 in the "control" group. Most of the latter received an antibiotic. There was one death which happened to be in the "control" group. Seventy-one percent of the test series and 79 percent of the "control" group were under 6 months of age. The drug was administered orally in divided doses totalling 3-5 mg. per Kilo body weight per day. It was initiated on an alternate case basis without waiting for laboratory results. When pathogenic organisms were found in the stools, *in vitro* sensitivity tests by the disc method were run against colistin sulfate as well as against other commonly used antibiotic and chemotherapeutic agents. Of 53 infants treated with colistin sulfate a positive stool culture for a pathogenic organism was found in 18 (34 percent).

Twenty-four very ill children, averaging 6.5 Kg. in weight, were treated with an oral preparation, colistin sulfate, in a dosage of 5 mg. base per Kg. per day, in divided doses (an average of approximately 32 mg. base per day). All were cured, the average time being 3.4 days. Sixteen other, more severely ill, children, with particularly persistent vomiting, were treated with colistin sulfate orally and sodium colistinmethanesulfonate intramuscularly. Their average weight was 6.2 Kg. The oral amount they received was approximately the same as that given to the first group. The intramuscular quantity was about 1.66 mg. base per Kg. per day (average of 10 mg. base per day). On this combined regimen, there were three failures (who also failed on various other treatments because of nutritional and additional factors), and twelve cures. The time for cure averaged 3.6 days. No relapses occurred when treatment was discontinued. No toxicity was noted in these treatments which were made by Hoekenga of the United Fruit Company, Panama.

► CYCLOSERINE and INH in childhood tuberculous infections were discussed by Schloss and Ismail of Metropolitan, and Bird S. Coler Hospitals, New York. Cycloserine's (CS) effectiveness has been amply authenticated. Its advantages are a low degree of bacillary resistance, effectiveness in the presence of bacillary resistance to the other remedies, and lack of toxicity in children, as shown by Lillick, *et al.* Unfortunately, CS' acceptance has been delayed because of undue fear of the neurotoxicity which occurs occasionally in adults, from large doses. Data was presented on 14 children with regressive tuberculous lesions despite previous intensive therapy. CS, 15 mg./Kg., and INH, 10 mg./Kg, daily, orally, promptly lowered the fever; body weight increased, and there was x-ray evidence of improvement in every case. There was only drowsiness in one child, who received 50 mg./Kg./day of CS inadvertently. Plasma level determinations assured satisfactory concentrations of CS. Based on the dramatic clinical response in all cases, including two with tuberculous meningitis, and lack of toxicity from effective CS doses, the authors recommend a CS with INH regimen as a first line of attack in childhood tuberculosis.

► DEMETHYLTETRACYCLINE, a member of a new family of antibiotics, was discussed by McCormick, Sjolander, Hirsch, Jensen, and Doerschuk of Lederle Laboratories.

A continuing investigation of the products accumulated by mutants of *Streptomyces aureofaciens*, Duggar, led to the discovery of one mutant, S-604, which in addition to chlortetracycline and a minor proportion of tetracycline, produced two new substances having appreciable antibiotic activity. They did not respond to the chemical assays for chlortetracycline and tetracycline but did appear to be tetracycline-related compounds when investigated by paper chromatography. Early results indicated that one of the new substances contained covalent chlorine and that the other was probably the corresponding unchlorinated derivative. Large scale fermentations and column chromatographic isolation of the two new components yielded yellow crystalline products which analyzed as $C_{21}H_{21}N_2C1O_8$ and $C_{21}H_{22}N_2O_8$, respectively, and which upon structural study were shown to be demethylchlortetracycline (DMCT) and demethyltetracycline (DMT). The loss of the C-6 methyl group of the tetracyclines had a profound effect on chemical reactivity towards acid and alkali, resulting in more than 100-fold stabilization in the case of DMCT as compared with chlortetracycline.

► DEMETHYLCHLORTETRACYCLINE has been compared with other tetracycline preparations by Boger and Gavin, Norristown State Hospital, Norristown, Pa. In small, carefully controlled groups of patients, DMCT has been compared with (a) chlortetracycline, (b) tetracycline hydrochloride in combination with citric acid, and (c) with tetracycline in combination with glucosamine. In 42 patients the diffusion of DMCT into the cerebrospinal fluid of patients with uninflamed meninges has been studied, following single oral doses of 500 mg. and 1000 mg. Administration of a small oral dose, four times a day, has demonstrated that DMCT is slowly excreted from the body and that there is actually a modest accumulation of the drug in the circulation during an average period of therapy. The usual daily dose of 0.6 Gm./day has been administered to a group of patients for 30 days, and no clinical side effects were observed and no significant abnormal findings were observed in the group. The finding that in equal amounts DMCT seems to exert a somewhat greater antibacterial effect than the other tetracyclines, suggests that there may be differential therapeutic effects following the administration of this antibiotic.

Forty-five patients hospitalized with a variety of clinical disorders, primarily bronchopneumonia and urinary tract infection, were treated with DMCT or DMCT with other antibiotics by Vineyard, Hogan, and Sanford of the University of Texas Southwestern Medical School, Dallas, Texas. The daily dosage was either 600 mg. or 1200 mg. administered for an average of 7 days. Clinical responses were satisfactory. Gastrointestinal toxicity was not observed on 600 mg. daily, though nausea was common on 1200 mg. daily. DMCT is a well tolerated tetracycline which shows *in vitro* activity which was equal to or greater than that of the other tetracyclines against 76 percent of "sensitive" strains.

Crossover studies were carried out in 11 healthy volunteers comparing serum antistreptococcal activity after ingestion of 0.3 Gm. of demethylchlortetracycline and 0.5 Gm. of tetracycline by Perry, Hall and Kirby of University of Washington School of Medicine and The King County Hospital in Seattle. Tetracycline produced higher levels of activity than demethylchlortetracycline at all time intervals measured during the first 24 hours. Among the 11 volunteers 7 experienced some gastrointestinal disturbance

after taking demethylchlortetracycline and only one after tetracycline. Strains of beta hemolytic streptococci, pneumococci, staphylococci and coliform micro-organisms, recently isolated from hospitalized patients are being studied to determine the MIC for demethylchlortetracycline and tetracycline. Preliminary results indicate that some, but by no means all, strains are more susceptible to demethylchlortetracycline. Fifty patients with acute respiratory or urinary tract infections have been or are being treated with demethylchlortetracycline. Sixteen of the patients received 0.3 Gm. twice a day and the rest 0.3 Gm. four times a day. The results indicate that demethylchlortetracycline has effective antibacterial action *in vivo*.

Studies performed with demethylchlortetracycline (DMCT) with regard to blood levels, accumulation in the tissues, urinary excretion, diffusion into the spinal fluid and clinical results in 70 cases of acute infections in children were reported by Fujii, Ichihashi, Minamitani, Konno and Ishibashi of the Tokyo University Branch Hospital. DMCT was compared with tetracycline hydrochloride, tetracycline with sodium metaphosphate and tetracycline with citric acid. The concentrations of DMCT in the blood were measured following administration of doses of 10 mg., 15 mg. and 25 mg. per kilogram of body weight, using *Escherichia coli* (NIHJ) and *Staphylococcus aureus* (209P) as test organisms. Blood levels of DMCT were found to be higher and longer-lasting than those of the other tetracyclines. In addition, DMCT showed markedly better accumulation in the tissues. Children with acute infections, including bacillary dysentery, were given 5 to 10 mg./Kg. of DMCT twice daily (12 hours apart). This treatment proved effective. (In cases of children with acute infection of the respiratory tract, the conditions were divided into those of viral etiology and those involving secondary bacterial infection.) Side effects were few in the patients receiving 10 mg/Kg. of DMCT. Gastrointestinal disturbances (vomiting and nausea) occurred in some of the patients given 15 mg. or more per kilogram of body weight.

Clinical trial of DMCT was undertaken by Marmell and Prigot of Harlem Hospital, New York. Included were 81 male patients with gonorrhea, 2 men with lymphogranulomatous buboes and 1 with donovanosis, and 2 women with rectal strictures secondary to lymphogranuloma venereum. In 62 gonorrhea patients who were adequately followed, the total dosage ranged from 300 mg. to 1 Gm. Satisfactory response was demonstrated clinically and confirmed by cultures in 60 cases. The 2 apparent failures were probably reinfections during the post treatment observation period.

Regression of lymphogranulomatous buboes occurred in 2 male patients after total dosages of 3.6 and 7.2 Gm. of DMCT, respectively. The lesion of donovanosis healed completely after the patient had received 7.5 Gm. of the antibiotic. In 2 women with lymphogranulomatous rectal strictures, inflammation subsided and the lumen of the constricted area increased in diameter in the course of therapy totalling 18 Gm. of demethylchlortetracycline. No toxicity or untoward reactions of any kind occurred in these patients.

Max of Mexico City studied the action of DMCT in 9 patients infected with *Brucella melitensis*, between the ages of 14 and 55 years. The doses used were 900 mg., every 24 hours in 7 patients and 1.2 Gm., in two of them. The treatment lasted for 45 days. Four of the patients complained of nausea and occasional vomiting spells that disappeared when the drug was administered with milk. The author concluded the DMCT has (1) A therapeutic effect on human brucellosis; (2) The therapeutic doses of this antibiotic are smaller than that needed for other tetracyclines; (3) The drug does not seem to produce side reactions; (4) Side effects do not warrant stopping treatment; and (5) There were no relapses.

DMCT was used in the treatment of 75 patients with genitourinary infections by Roberts, Seneca, and Lattimer of the Squier Urological Clinic, Columbia-Presbyterian Medical Center, New York City. Comparisons as to efficacy and antibacterial spectrums were made, between DMCT and tetracycline. Results revealed DMCT to be very effective against gram-positive organisms and to a lesser degree against gram-negative organisms. In every case the susceptibility of the infecting organism was as great (and usually one tube better) with DMCT as with tetracycline.

A variety of urinary tract infections were treated with demethylchlortetracycline with a regimen of 300 mg. t.i.d. for eight days by Trafton and Lind of Lind Laboratories, Brookline, Mass. Clinical response was good in most of the cases with relief of symptoms, elimination or marked reduction of pyuria, and with sterilization of urine in some cases. Dosage in all instances was less than 1 Gm./day, which was ½ to ⅔ the amount usually used for similar infections with other tetracyclines. This drug was well tolerated, less than 20 percent showing any evidence of intolerance. Side effects were minimal consisting mainly of mild diarrhea. Two cases showed excessive skin sensitivity on exposure to sunlight, one case resulting in sufficient erythema (sunburn) to cause hospitalization for treatment of the burn.

Duke, Donohoe, and Katz of the D. C. General Hospital and V.A. Hospital, Washington, D.C., presented a report based on the treatment of 32 cases of acute bacterial pneumonia with DMCT. Fifteen of these were uncomplicated pneumonias, nine were complicated by pleural, bronchial, or suppurative problems, and eight occurred in patients with underlying structural lung disease. A specific bacterial pathogen was isolated in 59 percent of the cases, with *D. pneumoniae* accounting for 47 percent of the total. DMCT was administered orally in a dose of 125 mg. every six hours. The therapeutic result was satisfactory in all except two cases. These pneumonias were due to organisms not susceptible to tetracycline drugs. One patient with pneumococcal pneumonia responded well initially, then developed a staphylococcal pneumonia and expired. Patient acceptance and tolerance were excellent, and no toxicity was encountered.

Lichter and Sobel, University of Illinois, Chicago, used DMCT in the treatment of 169 infections including 29 cases of pneumococcal pneumonia and 42 cases of scarlet fever. Four dosage schedules were employed: (1) 2 Gm. daily, (2) 1 Gm. daily, (3) 0.6 Gm. daily, and (4) 0.5 Gm. daily. The drug was given in divided doses every 6 hours. Multiple serum level determinations were performed during a course of treatment. At a daily dosage level above 0.6 Gm. daily a cumulative effect was seen with a median trough serum level range between 2.3 ug./ml. and 7.0 ug./ml. At 0.5 Gm. daily a cumulative effect was not seen and serum level remained about 2 ug./ml. with a minimal decline of serum level. DMCT penetrated into the cerebrospinal compartment poorly. Penetration into the pleural space was good. Milk and aluminum hydroxide gel were shown to inhibit gastrointestinal absorption. In general, clinical response was the same with the four dosage schedules. Of 29 patients with pneumococcoccal pneumonia, 15 were afebrile in 48 hours or less after starting therapy and all recovered except those with primary disease that caused death. Of 42 children with scarlet fever, 32 were afebrile in 48 hours or less after starting therapy and all recovered.

In the 98 other infections, response to DMCT was comparable to the previous experience with tetracycline antibiotics.

Hemopoetic, renal, and hepatic toxicity were not found. Gastrointestinal toxicity manifested by vomiting and/or diarrhea was seen in 67 percent of cases given 2.0 Gm. daily, in 12 percent of cases given 1.0 Gm. daily, and in 2 percent of cases given less than 0.6 Gm. daily.

Oral DMCT in the treatment of pustular dermatoses was discussed by Kanof and Blau of New York City. Sixty-seven patients with pustular dermatoses were treated with DMCT orally. Each patient took 150 mg. four times daily, and was observed at one or two week intervals for periods ranging from two to twelve weeks. Twenty-two patients had diagnoses of impetigo, hydradenitis suppurativa, pustular rosacca, folliculitis barbae, furunculosis and pyoderma complicating other dermatoses. Nineteen patients (86 percent) responded well. In the three patients who did poorly, bacterial studies showed the causative organism to be *Staphylococcus aureus*, phage type 80/81, very resistant to tetracycline. Forty-five patients had pustular acne vulgaris. Thirty-eight (84 percent) showed good improvement. Four patients developed nausea or diarrhea from demethylchlortetracycline. These side effects disappeared completely when the drug was discontinued. No pruritus ani or ulcerations about the mucous orifices, no urticarial or other drug eruptions occurred in this series of patients.

A comparison was made of the activity of demethylchlortetracycline and tetracycline against 40 strains of *Shigella*, 29 strains of *Salmonella* (other than *S. typhi* and *para A*), and 40 strains of enteropathogenic *Escherichia coli* by Olarte of the Hospital Infantil de Mexico. All cultures were isolated from children with diarrhea. Each strain was tested by the plate dilution method. The antibiotics were used at final concentrations ranging from 50 to 0.03 mcg./ml. Consideration was given to differences on the degree of inhibition of the bacterial growth observed in the streaks. Both antibiotics showed a similar activity against most of the cultures tested. Twenty four (60%) *Shigella*, 10 (34%) *Salmonella* and 17 (42%) *E. coli* strains were similarly resistant to demethylchlortetracycline and tetracycline, at concentrations of 10 mcg./ml. or more. One (3%) *Shigella*, 8 (28%) *Salmonella* and 7 (18%) *E. coli* cultures were inhibited by equal concentrations (ranging from 0.3 to 1.25 mcg./ml.) of both antibiotics.

In some instances (*Shigella* 37%, *Salmonella* 31% and *E. coli* 10%) a slightly higher activity was shown by demethylchlortetracycline than by tetracycline; in other strains (*Salmonella* 7% and *E. coli* 30%), a higher activity was obtained for tetracycline than for demethylchlortetracycline. However, the differences observed were apparently too small to be considered significant.

Four male volunteers were studied after receiving a single 150 mg. dose of DMCT by mouth. Periodic serum samples and all urine and stools were collected for a period of 104 hours after antibiotic administration. An identical procedure was followed in four subjects who received 150 mg. of DMCT by intravenous infusion. Direct comparisons of antibiotic recovery after the two routes of administration were made in three subjects who participated in both phases of the study. In another group of subjects, secretion of antibiotic activity into saliva was demonstrated and saliva levels are correlated with serum antibiotic concentration. Comparisons were also made of the serum antibiotic concentration which follows oral ingestion of 150, 250 and 500 mg. of DMCT. After both oral and intravenous administration, a large percentage of the antibiotic activity was recovered: oral—69 percent; intravenous—62 percent. After oral administration, 28 percent (range 9% to 43%) of antibiotic was recovered in urine and 41 percent (range 19% to 69%) was recovered in feces. After intravenous administration, 52 percent (range 48% to 54%) of antibiotic activity was found in urine and 10 percent (range 6% to 13%) in stools. The rapid appearance of antibiotic activity in feces after intravenous administration is suggestive of active large bowel secretion of antibiotic. Swallowed saliva could also account for a small part of antibiotic activity in feces, but the major pathway of excretion of DMCT into the gastrointestinal tract is assumed to be by the biliary tract. This study was reported by Sweeney, Dornbush, and Hardy of the Medical Research Section and Biochemical Research Section, Lederle Laboratories.

Sensitivities to 247 organisms were determined by Clapper and Proper of The Lovelace Foundation, Albuquerque, New Mexico. Serum levels were determined at 2 and 12 hours and daily on 10 patients given 250 mg. DMCT initially and 125 mg. daily thereafter. A cup plate method using *Bacillus cereus* was employed.

Results:

	No. of Strains	% Resistant	% more sensitive to DMCT
Coag. positive staphylococci	33	50	58
Streptococcus fecalis	12	41	43
Group A streptococci	12	8	81
B. coli	33	18	60
A. aerogenes	18	44	70
Proteus	22	82	82
Paracolon	13	8	60
Pseudomonas	12	33	87
Salmonella	24	12	80
Shigella	29	38	72

Differences in sensitivity could not be shown in those resistant to more than 25 ug., so these were omitted from the last column. Only 4 percent were more sensitive to tetracycline. As shown in the table, a high percentage of all groups are more sensitive to DMCT. This difference was usually twofold. Since the average of our daily serum levels was 2.0 ug./ml. and this is approximately the same as previously reported values for 250 mg. dose four times a day for tetracycline, it would appear that 125 mg. four times a day of DMCT might be expected to be twice as effective in most infections.

DMCT was used by Floyd and Anlyan of Duke University School of Medicine, Durham, N. C. in 60 surgical patients requiring an oral broad-spectrum antibiotic. These patients were divided into three groups: infected cases, contaminated cases, and cases in which prophylactic treatment was felt to be necessary. Cultures were taken in the first two groups and serial tube dilution sensitivity studies determined for all cultured organisms. No evidence of toxicity was manifested; therapy lasted between 5 to 15 days. There were no infections developing in the prophylactic or contaminated groups of patients. The majority of gram-positive and gram negative infections encountered to date have responded to treatment with this drug. DMCT appears to be a safe yet effective broad-spectrum antibiotic free of undesirable side effects.

DMCT, was the subject of clinical trial by Prigot, Maynard, and Zach of Harlem Hospital, New York, in 150 cases of acute soft tissue infections. The antibiotic was administered orally and was used alone or in conjunction with surgery where such intervention was necessary. Dosage was either 250 mg. 3 times daily or 150 mg. 4 times daily, for an average of 6 days' therapy. Laboratory studies established the safety of the antibiotic as the maximum dosage and duration produced no deleterious effects on the hematopoietic, cardiovascular, renal or hepatic systems. Mild gastrointestinal dis-

turbances which 3 patients reported did not necessitate interruption of medication. *In vitro* determinations confirmed the similarity between the antimicrobial spectra of DMCT and the parent drug, chlortetracycline. The clinical response to demethylchlortetracycline was excellent. The daily dose schedules and total medication were well below the levels employed in our studies of chlortetracycline, oxytetracycline and the tetracyclines in comparable cases.

The *in vitro* sensitivity to DMCT and the three other tetracyclines was determined for about 150 bacterial strains isolated from a representative group of acute infections by Tunevall and Frisk, Infectious Diseases Hospital, Bacteriological Central Laboratory of Stockholm City and Medical Service Ersta Hospital, Stockholm, Sweden.

The minimum inhibiting concentration of DMCT was about the same as for the other tetracyclines. Only occasionally did the difference in activity between the compounds exceed more than one dilution step. The absorption and renal excretion of DMCT after oral single dose of 0.5 Gm. were studied in three persons and compared with that of tetracycline in the same subjects. To a group of 30 patients, most of them suffering from urinary tract infections, 300 mg. DMCT was given every 12 hours for 4 to 7 days. The concentration in the blood was followed. Besides slight nausea in two cases no other side reactions occurred. In 65 percent of the patients with urinary tract infections sterile urine was obtained after demethylchlortetracycline therapy.

► DEXTROSULPHENIDOL was used in the treatment of experimental early syphilis in rabbits by Garson, Washburn, and Clark, U. S. Public Health Service, University of North Carolina, Chapel Hill. This disease is apparently cured by a total dose of dextrosulphenidol of 25 mg./Kilo. This compares very favorably with chloramphenicol, which produces cure in experimental syphilis at a total dose of 200-800 mg./Kilo.

► DIAZOMYCINS (BA-8509) A, B, and C are three antitumor substances. The organism *Streptomyces ambofaciens* yields broths which show activity of a high order against Sarcoma 180 and Adenocarcinoma 755 in mice. The active principle is found to consist of four related substances which belong to the general class of aliphatic diazo ketones. One of these four is shown to be identical with 6-diazo-5-oxy norleucine (DON). The method of isolation consists of concentration of the broth to 10 percent of its volume, dilution with 9 volumes of methanol followed by filtration. The filtrate is concentrated to remove most of the solvent, diluted with water and run through a column of activated carbon. Elution with aqueous acetone yields the crude starting material. The next step is the rough separation of the components by an ion exchange procedure. Passage through Dowex-1 (acetate) yields the 6-diazo-5-oxy norleucine in the effluent while the other three remain on the column. Elution with dilute phosphate buffer gives diazomycins A, B, and C in that order. Further separation of diazomycins A and B has been achieved by a repetition of the ion exchange procedure. The separated components are individually subjected to countercurrent distribution in the system phenol-water whereby they are obtained pure and subsequently crystallized. Separation of diazomycins B and C is effected by counter-current distribution in the system phenol-water in which they are well separated from each other. The C-component is separated and crystallized. Diazomycins show a characteristic ultraviolet spectrum similar to that shown by DON and alazopeptin and their infrared spectra show the band also characteristic of the aliphatic diazo ketones. They are highly unstable in solutions below *p*H 5.5. Diazomycins show high activity in mice against Sarcoma 180 and Adenocarcinoma 755 and diazomycin B shows a moderate activity against L-1210, according to Rao, Brooks, Kugleman, and Romano of John L. Smith Memorial for Cancer Research, Maywood, New Jersey.

► DIHYDROSTREPTOMYCIN deafness was discussed by Harrison of Chicago. During the last five years, many papers have been published dealing with the ototoxicity of dihydrostreptomycin, but in practice, case after case is still seen with irreversible hearing loss due to the use of this drug, usually in combination wtih penicillin and streptomycin. Because of the known toxic effect of streptomycin on vestibular function and the known toxic effect of dihydrostreptomycin on the cochlear function, these drugs have been combined with the idea that with a small dosage of each, the toxic effect of each would be eliminated. Often these combinations are marketed under names that do not clearly indicate the presence of dihydrostreptomycin. Many cases are seen where such combinations have been given, not as life-saving measures but prophylactically and for mild infections. The result has too often been irreversible nerve deafness. Dihydrostreptomycin is particularly treacherous because of the small dose necessary to produce this hearing loss and because of the latent period between administration of the drug and the onset of the loss. Many cases of moderate or mild loss in pure tone from the use of this drug are accompanied by a disproportionate impairment of speech discrimination. There is no known effective treatment for this loss. It is recommended that this antibiotic be omitted from commercial combinations of antibiotics, or if included, its presence should be clearly indicated in the name.

► DIHYDRODESOXYSTREPTOMYCIN and its effect on the function of the eighth nerve were discussed by Christensen, Herrell, and Gilboy of Lexington Clinic and Julius Marks Sanatorium, Lexington, Kentucky. Preliminary studies previously reported suggested that the use of dihydrodesoxystreptomycin was associated with less toxicity than the previously available forms of streptomycin. In order to test the possible effect of dihydrodesoxystreptomycin on the function of the eighth nerve, a study was undertaken. Nine patients under observation and treatment for tuberculosis were included in the study. The patients selected ranged in age from 20 to 77 years. Each patient received 1 Gm. of dihydrodesoxystreptomycin by the intramuscular route daily for three months (90 days). Pre-treatment vestibular function studies and audiograms were performed on all patients. These studies were repeated 30, 60 and 90 days after treatment was initiated. After 90 days of treatment with dihydrodesoxystreptomycin there was no evidence of impairment of function of either the vestibular or auditory function of the eighth nerve in these patients, as determined by the methods employed.

Almeida and Almeida of the Laboratories Atral, Lisbon, Portugal reported studies on the streptomycin methioninates. The authors studied the following products: mixture in equal parts of streptomycin and dihydrostreptomycin methioninates (SM), mixture of 50 percent S.M. and streptomycin and dihydrostreptomycin sulfates, and the mixture of 20 percent S.M. and streptomycin and dihydrostreptomycin sulfates. The S.M. and the 50 percent mixture are ill tolerated provoking pain at the site of injection.

The experiments were continued using only the 20 percent mixture. This has been well tolerated when injected daily and in a dosage equivalent to 1 Gm. of streptomycin by 38 of 44 patients who had previously shown intolerance to the

latter drug, in a total dosage averaging about 150 Gm. In equal concentrations streptomycin methioninate appears superior to the streptomycin pantothenate and deserves a place in the treatment of tuberculous patients with intolerance of streptomycin.

► ENZYME THERAPY in pulmonary diseases was discussed by Shubin, Rush Hospital, Wolffe Hospital, Philadelphia General Hospital, Northern Division, Philadelphia. The proteolytic enzymes, both of streptococcal (streptokinase and streptodornase) and pancreatic (trypsin) origin have proven beneficial in the treatment of varicose ulcers, thrombophlebitis, etc. They have been shown to liquefy thick mucus, to increase permeability of tissue and have anti-inflammatory action, so that their use in pulmonary diseases seemed indicated.

These complete studies in 125 patients began in 1955 with parenteral streptokinase and streptodornase (Varidase) and trypsin in oil (Parenzyme), which produced minimal clinical improvement but were too toxic. In 1957, buccal Parenzyme was evaluated, also with some beneficial clinical results but with too much local (oral) irritation. In 1958-59 trypsin aqueous (Parenzyme), and an oral trypsin (Orenzyme) were given to patients suffering with lung abscess, chronic bronchitis, chronic bronchial asthma, pulmonary emphysema, bronchiectasis and pulmonary tuberculosis. Parenteral aqueous trypsin was given intramuscularly (1 ml.) daily for one week, then every other day for two weeks. Four to eight tablets of Orenzyme were taken daily for 4 to 6 weeks. Marked or moderate improvement was found in 65 percent of these patients. There was a minimum of toxicity with the parenteral trypsin, slight local but no systemic reaction, and no incompatibility with other drugs. The oral trypsin, with its ease of administration, and very good clinical results, seems most promising. These results indicate that trypsin, parenteral aqueous or oral, has a definite place in our therapeutic armamentarium against pulmonary infections.

► ERYTHROMYCIN PROPIONATE in general infections was the subject discussed by Shubin of Germantown Hospital, Rush Hospital and Wolffe Hospital, Philadelphia. In 103 patients with infections due to nine common organisms, good results were obtained in 97, with minimal side effects. Thirty-nine of these patients were hospitalized, while the remainder were outpatients. The majority of cases received 500 mg. every 6 hours for one to two days, followed by 250 mg. every 6 hours for 5 to 70 days. All patients were followed for four to six months with relapse in four cases, two of whom responded to erythromycin propionate and two (erythromycin-resistant) responded to triacetyloleandomycin. This study indicates that the erythromycin ester is much more reliable and effective than its base.

Effectiveness of oral erythromycin propionate in commonly occurring infections was discussed by Calesnick of Hahnemann Medical College, Philadelphia. A group of 127 patients with upper and lower respiratory infections, pyodermias, apical abscesses, enteritis or pyelonephritis was administered this drug by mouth. Of this number, 84 patients had a bacteriological evaluation and the predominant organisms were alpha and beta hemolytic streptococci and *Staphylococcus aureus*. The *in vitro* sensitivity of these organisms to erythromycin varied between 76.5 and 96.3 percent. The most sensitive organism was alpha hemolytic streptococcus which had an incidence of 27.2 percent. On the other hand, 81.9 percent of all organisms isolated were erythromycin-sensitive. Erythromycin propionate was administered only to patients who had erythromycin-sensitive organisms and 6 therapeutic failures were found in individuals who were "carriers." In the group which did not have a bacteriological survey, the "complete cure" rate was 67.4 percent; "partial cure" was an additional 28 percent. The side effects encountered were principally of the gastrointestinal variety in 4.7 percent. In contrast to the reported higher incidence of side effects encountered with erythromycin base, this ester offers a definite advantage in its clinical usefulness.

Cronk and Naumann of Syracuse University, Syracuse, N. Y., reported results of treatment of 246 patients with acute infections with erythromycin propionate and found that no definite advantage could be determined for using 500 mg. doses rather than 250 mg. doses.

In contrast, Marmell and Prigot of Harlem Hospital, New York, determined the therapeutic potential of oral erythromycin propionate for acute anterior gonococcal urethritis and reported the optimum dose schedule to be 500 mg. four times a day for 4 days.

A clinical and laboratory evaluation of erythromycin propionate was carried out by Isenberg, Karelitz, and Stillerman of The Long Island Jewish Hospital, New Hyde Park, N. Y. The drug was given orally to 121 patients, contacts and carriers in doses of 30-40 mg./Kg./day to children who comprised the greater number of individuals in this study and 1 Gm./day to adults. A variety of clinical infections due to *Streptococcus pyogenes* group A, *Staphylococcus aureus, Diplococcus pneumoniae, Hemophilus influenzae,* members of the family Enterobacteriacae and other bacteria were encountered. The results were good in 102, good but with recurrence in 5 and in 14 no improvement could be established. Toxic symptoms usually were not severe. However, the drug had to be discontinued in 5 children, in 3 because of severe vomiting, in one because of abdominal cramps and one other because of nausea. Diarrhea, nausea and abdominal discomfort were experienced by many of the adults especially when on doses in excess of 1 Gm./day. Only in one case were symptoms so severe that therapy was discontinued.

► FERVENULIN, a new, crystalline antibiotic, was reported by DeBoer, Dietz, Eble, Evans, Michaels, Olsen, Large, and Shell of the Research Laboratories, The Upjohn Company, Kalamazoo, Michigan. Fervenulin was isolated from a species of soil actinomycete, *Streptomyces fervens,* n. sp. A submerged fermentation medium was described in which *S. fervens* produces 100-200 ug./ml., assayed by the standard agar diffusion plate method using *Klebsiella pneumoniae* as the test organism. By papergram analysis, culture filtrates of *S. fervens* were shown to contain a new active component, fervenulin, with an Rf of 0.45 in a 1-butanol-water (84:16 volume ratio) system containing 0.25 percent *p*-toluenesulfonic acid. Fervenulin exists as yellow orthorhombic crystals which melt at 178-179°C. The molecular formula is $C_7H_7N_5O_2$. The antibiotic demonstrated antibacterial, antifungal, antiparasitic and antitumor cell activity *in vitro*. The LD_{50} of fervenulin in mice was 65 mg./Kg., I.P., while the CD_{50} against *Trichomonas vaginalis* and *Trichomonas foetus* in mice was 5 mg./Kg., I.P. However, fervenulin showed little activity *in vivo* against bacteria, fungi and tumors.

► FURALTADONE, a new nitrofuran, was evaluated by McCabe and Jackson of the University of Illinois College of Medicine, Chicago. The continuing problem of staphylococcal infections has given impetus to the search for new antistaphylococcal agents. A nitrofuran, furaltadone (5-morpholinomethyl, -3- (5-nitrofurfurylideneamino) -2- oxazolidinone) was reported to be inhibitory *in vitro* for strains of staphylococci and beneficial in experimentally induced

staphylococcal infections. Forty strains of staphylococci well studied for sensitivity and resistance to other antibiotics were tested for sensitivity to furaltadone by the serial tube dilution method. All were inhibited by concentrations of furaltadone over the range of 1.2 to 18.8 ug./ml. No evidence of cross-resistance with other antibiotics was noted. Consecutive colony counts gave evidence of bactericidal activity at inhibitory concentrations of the drug. *In vitro* resistance to 250 ug./ml. was readily induced by 6 to 13 serial passages through media containing sub-inhibitory concentrations of furaltadone. No staphylococcal strains with more than moderate resistance to furaltadone were isolated from clinical material.

Among patients treated with furaltadone, detectable blood levels were found in only one-third of the samples taken at varying intervals after oral administration of 200 mg. every four to six hours. In those specimens with activity, maximum serum levels appeared in the samples two hours after administration of a dose. Less than 20 percent of the specimens demonstrated any drug level six hours after an oral dose of 200 mg. Clinical and bacteriologic response tended to parallel the serum drug levels. Some untoward reaction was observed in one-half of the patients receiving furaltadone and were severe or potentially severe in about 10 percent.

► GRISEOFULVIN, its metabolism and mechanism of action, were discussed by McNall of the University of California Medical Center, Los Angeles. Studies in experimental animals have shown that griseofulvin is absorbed largely unchanged in chemical form and that the compound is biologically active in blood, serum and various tissues. The characteristic absorption pattern in mice shows a maximum level of the antifungal agent between 5 and 8 hours following oral administration. The levels at 2 and 24 hours are considerably lower and are subject to greater variation.

Robinson of Washington, D. C. reported on the systemic treatment of superficial mycoses with griseofulvin. Since the trichophyton group and *Candida albicans* are responsible for the majority of superficial mycoses and adequate antibiotic therapy is available for treatment of candidiasis, this drug is an important inclusion in the list of antimycotic agents. Twenty-five patients with superficial mycoses of proven trichophyton origin, other than *Tinea capitis,* make up this experiment which also includes toxicity studies. Griseofulvin was administered in doses of 1 Gm. daily. Patients were seen once or twice weekly. In all cases where treatment was continued without interruption therapy was effective. In one case there was a recurrence six weeks after medication was discontinued. With the exception of one case in which there was an increased icterus without symptomatic jaundice, no significant side effects were seen on a laboratory level. There was some complaint of gastric distress which disappeared while the drug was still being administered. In one case psychic stimulation necessitated the stoppage of the drug. No cases of urticaria were observed in this series in spite of the fact that a few patients were known to be sensitive to penicillin.

A paper by Johnson and Cameron dealt with experiences at the University of Wisconsin Hospitals in the use of griseofulvin, a fermentation product of three species of penicillin (P. patulum, P. griseofulvin, P. janczewskii) which is currently being used orally in the treatment of superficial mycoses in more than 30 patients. The dosage schedule, in the main, was 2.0 Gm. daily for eight weeks and 1.0 Gm. daily thereafter. The majority of the patients had *Trichophyton rubrum* involvement and many had onychomycosis, an entity refractory to treatment prior to the introduction of this orally effective antifungal agent. The results thus far have been most encouraging. All of the patients have improved and toxicity studies indicate no concurrent changes other than a variation in the sperm counts; some have increased whereas others have decreased. This aspect is under continued observation. This dosage schedule was possibly twice the amount that will come to be the accepted therapeutic dose. Although final conclusions cannot be yet reached, it appears that griseofulvin, according to these studies, is not toxic in even twice the therapeutic dose and attests to its margin of safety.

Dermatomycoses were treated with griseofulvin by Goldfarb and Rosenthal of New York University Hospital, New York. In order to properly evaluate the clinical efficacy of this drug, the data was grouped in the usual dermatologic subdivisions (*Tinea capitis,* onychomycosis, *Tinea cruris,* etc.). The usual dosage was 1 Gm. per day with a range of 0.25 to 2 Gm. per day. The patients were observed for two weeks to nine months. Mycologic as well as hematologic and other laboratory studies were performed at intervals during the course of treatment. *Tinea cruris* and other glabrous lesions responded most rapidly. Decrease in itching was the first subjective sign of improvement noted. Hyperkeratotic lesions of the palms and soles responded more slowly. Infected hairs and nails showed slow, steady progress, relative to their natural rate of growth. Side reactions were minimal. Hematologic and other laboratory tests were within normal limits. For comparison, the response of patients with dermatomycoses treated only by topical medication was followed. Griseofulvin has proven to be of definite therapeutic value in the treatment of superficial ringworm infections, especially so in those of a previously inveterate nature.

Ninety-seven children were treated for *Tinea capitis* with griseofulvin by Behrman, Lubowe, Mandell, Morse, and Baker of New York Medical College New York. Ninety-six were infected with *M. andouini,* one with *M. lanosum.* Eighty-eight were males and nine females. Age limits were from one and one-half to twelve years. The earliest negative culture was observed after four weeks of therapy. The latest negative culture was demonstrated thirteen weeks after therapy. The smallest quantity of griseofulvin to produce negative culture was three tablets of 250 mg. The largest quantity of griseofulvin necessary to present the negative culture was 168 tablets of 250 mg. The only untoward reaction observed was diarrhea and epigastric pain in one child, which disappeared on continuance of therapy.

► HUMYCIN was studied in 55 cases of diarrhea in infants and children by Godenne of The Johns Hopkins Hospital, Baltimore. The children were given 50 to 100 mg. per Kg. per day for a period of 6 days and stools (rectal swab) were cultured the 1st and 4th day of treatment. Among the 18 cases of diarrhea due to Salmonella or Shigella, 7 had negative stool cultures for these organisms after 4 days of treatment. Among the 39 cases with complete laboratory data, 7 had negative cultures for all organisms after 4 days of treatment. No clinical ill-effects of the drug were noted.

► ILENTAZOLE is a molecular complex, consisting of 8-hydroxyquinoline and the phthalyl sulfathiazole fractions, each active against specific groups of microorganisms. The first component is primarily fungistatic, while the second represents the bacteriostatic factor. Reports indicate that the complex molecule, in conditions simulating those of the gastrointestinal tract, dissociates into the 2 original fractions. To determine its effect on aerobic intestinal flora, this medication was administered orally to 9 hospitalized patients. Five received a total of 2 Gm. and 4 received 4 Gm., given in 4 equal doses for 1 day only. The total aerobic count was

reduced numerically under both dosage schedules. However, the larger dose demonstrated a more consistent and greater suppressive effect. Both gram-negative and gram-positive flora, in general, were inhibited to an equal degree, while staphylococci were depressed to a lower level by the larger dose. On fungi an unexpected result was detected in that the lesser quantity of Ilentazole produced an average numerical reduction which was greater than that of the larger dose. None of the patients exhibited or complained of any untoward reactions during or after therapy. These studies were reported by Shidlovsky and Prigot of Harlem Hospital, New York.

► KANAMYCIN in the management of infections was discussed by Koota and Rutenburg of Beth Israel Hospital and Harvard Medical School, Boston. They reported on the use of kanamycin in 163 patients with a variety of infections due to staphylococci as well as various other gram-positive and gram-negative bacteria. Kanamycin has a wide antibacterial spectrum which included staphylococci resistant to other antibiotics. Infections due to Staphylococci, *E. coli,* and *A. aerogenes* were particularly susceptible to therapy with kanamycin. One hundred thirty-nine of the 163 patients with infections of the postoperative wounds, soft tissues (primary), respiratory tract, peritoneum and the blood stream including 69 who had failed to respond to prior antibiotic therapy showed a favorable response to kanamycin therapy. The drug toneally in appropriate situations. Kanamycin was well tolerwas administered intramuscularly, intravenously, and intraperiated. There were 14 reactions including cylindruria in 13 and transient renal insufficiency and permanent partial hearing loss in the 14th patient. No other evidence of systemic or local toxicity was encountered.

A significant diminution of the acute toxicity of kanamycin obtained by using pantothenate instead of sulfate was reported by Lagler, Osterloh, and Muckter of Chemie Grunenthal, Stolberg Rhld., Germany. Addition of calcium and increasing the *p*H diminishes the acute toxicity of both kanamycin compounds. Experiments in semichronic toxicity equally showed a significant superiority of certain kanamycin pantothenates over the sulfate. Long-term subcutaneous treatment with 400 mg./Kg. kanamycin pantothenate and sulfate respectively did not bring about disturbances of vestibular function tested on mice, rats and guinea pigs, whereas the same doses of streptomycin sulfate caused marked vestibular injury.

Using various test methods on rats and guinea pigs it was possible to demonstrate the specific chronic toxicity of kanamycin sulfate towards the cochlear nerve. These cochleotoxic side effects could significantly be reduced by using pantothenic acid. High doses of kanamycin sulfate given over long periods in animal experiments cause reversible renal damage, and it appears that the nephrotoxicity of kanamycin cannot substantially be influenced by pantothenic acid.

The excretion of kanamycin in bile and pancreatic fluid was reported by Silverman, Preston, Neveril, and Henegar, Departments of Surgery and Bacteriology, V.A. Research Hospital and Northwestern University Medical School, Chicago. Maximum serum levels of the antibiotic equaled 20 to 24 ug./ml. and were obtained 1 or 2 hours after injection. Maximum levels in bile were observed 3 to 8 hours after injection, and occurred several hours after maximum serum levels. In three patients with normal liver function the maximum levels in bile were about equal to maximum serum levels. In one patient with marked impairment of hepatic function the highest concentration of kanamycin in bile was approximately one-half the highest serum level. The highest level observed in pancreatic fluid was 5 ug./ml. and amounted to 25 percent of the highest serum level. It was observed 6 and 8 hours after injection. Total amounts of kanamycin recovered in bile were less than 0.5 percent of the total dose given. The recovery in pancreatic fluid was less than 0.01 percent of the total dose.

Kanamycin does not penetrate the spinal fluid barrier under normal conditions according to studies reported by Dube of the Van Duyn County Memorial Hospital, Onondaga, New York.

Intraperitoneal use of kanamycin in established peritonitis and peritoneal contamination was discussed by Prigot, Campbell, and Maynard of Harlem Hospital, New York. Since a preliminary report, additional patients have been successfully managed with this technique, bringing the total for established peritonitis to 39 cases and for peritoneal to 68.

The wide antimicrobial capacity of kanamycin has been adequate to meet the challenge of bacteria found in the peritoneal cavity in these critical situations. The antibiotic had no deleterious effect on the peritoneum and in patients undergoing subsequent operations few adhesions were found. When correctly employed, the danger of respiratory arrest from kanamycin is minimized.

Intramuscular kanamycin was employed for the treatment of gonorrhea. Marmell and Prigot of Harlem Hospital, New York reported the results in a total of 124 patients receiving kanamycin at various dosage levels. The disappearance of clinical symptoms of infection and negative findings in 3 follow-up cultures in a period of a week after treatment were the criteria of cure. Twenty-five patients who received 3 Gm. of kanamycin by intramuscular injection in 3 days were cured. There were 8 failures among 35 patients who received 2 Gm. in 2 days. However, a total dosage of 1.5 Gm. administered over a 3 day period produced 54 cures in 56 trials. Since the total dosage for the successful treatment of gonorrhea is well below the levels at which kanamycin toxicity may be encountered, there were no untoward side effects in the series.

Susceptibility of *Staphylococcus aureus* to kanamycin, vancomycin, neomycin, and novobiocin was discussed by Greer and Menard of Henry Ford Hospital, Detroit. Over 800 organisms from more than 320 patients and hospital personnel were tested for susceptibility to vancomycin, kanamycin, neomycin, and novobiocin by the disc technique. None was resistant to vancomycin or kanamycin. Rarely has any *S. aureus* shown resistance to neomycin, but a few (less than 4%) were hyposusceptible to novobiocin. Over 150 determinations of novobiocin susceptibility by the broth dilution technique have been made.

► MITOMYCIN C is one of the principal antitumor antibiotics produced by a strain of soil fungi, *Streptomyces caespitosus.* Shiraha, Sakai, Hashima, and Fukusumi of the Osaka City University Medical School, Osaka, Japan, treated 112 cases of malignancies with either intravenous or intraarterial mitomycin C in the field of general surgery. Of the total of 194 cases, 151 were inoperable advanced malignancies and the remaining 43 were placed on intravenous mitomycin C postoperatively to prevent either metastasis or relapse. Three cases of the advanced malignancies have been doing excellently 20 months (cancer of the maxilla), 16 months (stomach cancer after gastrojejunostomy) and 10 months (cancer of the urinary bladder) respectively after completion of the drug administration, and 24 out of 27 cases who had been placed prophylactically on mitomycin C are uniformally free from recurrence more than 6 months (5 cases more than 20 months, 11 more than 13 months and 6 more than 6 months). The authors analysed and discussed the results of

evaluation of mitomycin C obtained on 663 malignancies accumulated in Japan during the past one year. Leucopenia and bleeding tendency, mainly caused by thrombocytopenia are most serious side effects encountered in mitomycin C therapy, but controllable and curable under careful use of the antibiotic.

Experimental evidence obtained within the last few years has indicated that certain antibiotics have strong antitumor effects on specific animal neoplasms. Such studies continue to yield new information which may be applicable for possible trial against human cancer. The first intraperitoneal injection of the antibiotics at maximum tolerated doses was given 1-7 days after tumor transplantation and injections were continued for 7 days. Mitomycin C was possibly the most effective antibiotic among twenty nine purified or crystalline antibiotics tested, followed by fumagillin, 6-diazo-5-oxo-L-norleucine, actinomycins C, D and J, actinobolin, sarkomycin and streptovitacin A, according to Sugiura of the Sloan-Kettering Institute, New York.

► NEOMYCIN in combination with other agents was used in the treatment of cutaneous infections by Olansky of Duke University Medical Center, Durham, N. C. A topical preparation containing 0.1 percent triamcinolone acetonide plus 2.5 mg. neomycin, 0.25 mg. gramicidin, and 100,000 units nystatin per gram of vanishing cream or oleaginous ointment base was found to be a safe and highly effective treatment for primary or secondary cutaneous moniliasis and other infected skin lesions when applied 4 times daily for periods ranging from one week to one month. Oral nystatin was administered concomitantly where cutaneous manifestations of moniliasis were secondary to intestinal disease and where local treatment of perianal areas could be benefited by clearing the intestinal tract of *Candida albicans*, thereby removing the major source of re-infection.

Treatment of cutaneous candidiasis and pyoderma, primary or secondary to other skin pathology, with the same combination resulted in an early subsidence of the active infectious process, itching, and inflammation followed by a progressive involution of the underlying eruption according to another report by Howell of Wake Forest College, Winston-Salem, N. C.

► OLEANDOMYCIN combined with tetracycline was used in the treatment of burns by Garre of the Medical School, University Litoral, Rosario, Argentina. Daily oral dosage oscillated between 1.0 and 2.0 Gm. in adult patients; in children the average was 500 mg. The author concludes that tetracycline-oleandomycin is of extraordinary therapeutic value in the prophylactic and medical treatment of burns.

Treatment of contagious syphilis with a combination of oleandomycin-tetracycline was reported by Prats and de la Parra of the University of Chile, Santiago. The course of therapy for all patients was 2 Gm. daily given in 4 equally divided doses at 6 hour intervals for 10 days. The combination was judged extremely useful in the treatment of syphilis, including cases in which there is an associated lymphogranuloma venerum, because of the extremely low incidence of side effects and their mildness.

Clinical efficacy of an oleandomycin-tetracycline preparation in pediatrics with particular reference to severe infections was reported by Schweier of the Children's Hospital, Schwabing, Munich, Germany. In some cases it was necessary to extend the average dosage of 20-50 mg./Kg. to 80-100 mg./Kg. per day which was well tolerated without side effects during a rather long period of time, with the exception of one case showing an allergic exanthema. The very best method of initiating therapy in most serious infections such as staphylococcal sepsis, osteomyelitis, serious staphylococcal pneumonia, empyema, meningitis purulenta, extended phlegmonous processes was by means of a drip-enema. This method is a convenient one for use in the smallest of infants. The efficacy of this method of treatment, having been employed in approximately 100 cases is an effective one and assures a broad range of clinical action. It is the opinion that the oleandomycin-tetracycline formulation used in this way, offers clinical benefits superior to the oral administration of all other antibiotics.

Studying the emergence of resistant strains of staphylococci, Torra and Saldana Tate of Hospital Pasteur, Montevideo, Uruguay, found that there is a great variability in the metabolic responses of the same strains of staphylococci in acquiring resistance, and that there is a delay in the emergence of resistance with the combination of the drugs oleandomycin and tetracycline.

► OXYTETRACYCLINE, results of 10 years of use, was discussed by Musselman, University of Nebraska College of Medicine, Omaha. Since its discovery and isolation in 1949, oxytetracycline has been used successfully in the treatment of a wide variety of infectious diseases because of its broad range of activity against bacteria, spirochetes, rickettsiae, large viruses, actinomycetes, and even some protozoa and metazoa. In order to determine whether the passage of time has altered the efficacy of oxytetracycline appreciably, a survey of the American and foreign medical literature, published in the English language, was conducted by the New Drug Institute, Inc., under the direction of Arthur D. Herrick. The survey which covered more than 500 clinical papers listed in the Current List of Medical Literature and the Index Medicus determined the number of patients who have received oxytetracycline, the indications for therapy, dosages, durations of treatment, responses to therapy, and incidence and types of untoward reactions. The results of the survey indicate that the practical effectiveness of oxytetracycline has not been appreciably reduced and that its incidence of untoward effects is approximately that of other available broad-spectrum antibiotics.

Tissue diffusion of oxytetracycline measured by fluorescent studies in patients with osteomyelitis and in experimental infections was reported by Plaza-Roca of the Police Hospital, Lima, Peru. In 1957, the author observed that a solution of oxytetracycline produced a fluorescence when placed on filter paper. The significance of this observation was not fully comprehended until more recently when it was observed that this fluorescence was present in bones of patients who had been administered oxytetracycline for the treatment of infection. Determined by the persistence of the fluorescence, oxytetracycline is fixed in bone substance for an appreciably long time. In addition, the fluorescence is far more marked in bone tissue which has undergone osteogenic change. In experimental studies, a similar development takes place. The same is true, also, in normal human subjects. In patients who have had osteomyelitis, to whom oxytetracycline is given and the infection responds clinically, the fluorescence observed in the areas where bone has been regenerated is surprisingly high and is markedly more evident than in the areas of the bone which were not infected. The author suggests the calibration of this effect and its application into clinical therapy or other areas of research so that diffusion observations can be more definitively evaluated. Such a development can be particularly recommended because the method is simple.

► PAROMOMYCIN, an antibiotic of *Streptomyces* origin, has been examined extensively for evidence of microbiologic

activity *in vitro*, pharmacologic characterization in laboratory animals, and therapeutic efficacy in man. *In vitro*, the substance proved to be highly effective against *Entamoeba histolytica* and a wide variety of bacteria; its amebicidal potency was equal to that of emetine and it appeared to affect amebae directly. When given by mouth to animals the substance was very non-toxic and absorbed negligibly from the gastrointestinal tract. It exhibited excellent therapeutic activity against experimental intestinal amebiasis in rats and dogs. Parenteral doses had strong therapeutic effect against amebic hepatitis in hamsters and several types of systemic bacterial infections in mice, but the drug has some nephrotoxic liabilities when given parenterally. Therapeutic trials of paromomycin orally in over 1000 patients have demonstrated that it is tolerated extremely well, is remarkably effective against both chronic and acute intestinal amebiasis, and has good therapeutic action against many types of bacterial enteritis. The laboratory and clinical data indicate paromomycin to be unique among known antibiotics to the extent that it is characterized by low oral toxicity coupled with high antiamebic and antibacterial activity, according to Courtney and Thompson of Parke, Davis and Company.

A series of experiments were performed by Fisher, Manning, Gagliardi, Gaetz, and Erlandson of Parke, Davis and Company to delineate the behavior of paromomycin against medically important bacteria *in vitro* and *in vivo*. This antibiotic was shown to be bacteriostatic, at less than 10 ug./ml., against a wide variety of bacteria *in vitro*. Paromomycin was especially effective against staphylococci and gram-negative bacilli as an inhibitor *in vitro* and in experimental infections in mice. This antibiotic also exhibited marked bacterial activity *in vitro* and *in vivo* under severe test conditions. Paromomycin given parenterally was moderately tuberculostatic in mice and guinea pigs.

► PENICILLIN REACTIONS were discussed by Brown, Simpson, and Price of the Communicable Disease Center, Atlanta, Georgia. In 1954, the Public Health Service conducted a study of penicillin reactions among patients in venereal disease clinics throughout the United States. The initial study covered the months of April, May, and June, but was later extended to include a more representative sample of benzathine penicillin G. A total of 19,510 records of patients treated with penicillin were collected. Reactions to penicillin were reported in 116, or 5.95 per 1,000 treated.

Since penicillin is the principal weapon in the fight against syphilis and gonorrhea, the increasing awareness of penicillin sensitivity and the report of several deaths among venereal disease patients prompted a re-evaluation of the situation. Another study, identical as far as possible to the one in 1954, is in progress at the present time. To date, records have been received on 20,687 patients treated with penicillin since March 1959. Reactions have been reported in 206, or 9.96 per 1,000 treated.

► ALPHA-PHENOXYETHYL PENICILLIN was isolated as the potassium salt and designated BL-P152 by Perron, Crast, Gottstein, Minor, and Cheney of Bristol Laboratories, Inc., Syracuse, N.Y. Because of the presence of the asymmetric center in the side chain, BL-P152 is a combination of two diastereoisomeric forms. Each of the diastereoisomers has been synthesized in essentially optically pure form and has been found to possess distinctive physical properties, including marked differences in specific rotation, solubility and the "finger-print" region of the infrared spectrum. Resolution of DL-alpha-phenoxypropionic acid was accomplished through the yohimbine salt. The mixed anhydride procedure was used to advantage for the N-acylation of 6-APA (6 aminopenicillanic acid) with the optically pure alpha-phenoxypropionic acids. Concurrent racemization was thus held to a minimum. On the basis of convincing stereochemical evidence it is highly probable that the configuration of dextro-alpha-phenoxypropionic acid is sterically related to D(-)-lactic acid. For this reason the diastereoisomer derived from D(+)-alpha-phenoxypropionic acid has been designated BL-P152-D, and the diastereoisomer obtained from L(-)-alpha-phenoxypropionic acid is referred to as BL-P152-L.

The (L-alpha -phenoxyethyl) penicillin was found to be more active than the (D-alpha -phenoxyethyl) penicillin with most organisms as judged by *in vitro* tests. The mixture is at least as active as the pure (L-alpha-phenoxyethyl) penicillin. The minimum inhibitory concentration obtained with the isomeric mixture against a wide variety of organisms is similar to that obtained with penicillin V. The penicillin is considerably more resistant to *Bacillus cereus* penicillinase than penicillin G or V. It is approximately as acid stable as penicillin V. The penicillin inhibits clinically resistant strains of staphylococci at lower levels than penicillin G or V. It behaves similarly to penicillin G and V with regard to serum binding, influence of *p*H, and influence of media. In animal protection tests using *Staphylococcus aureus* as the infecting organism, potassium (alpha -phenoxyethyl) penicillin is consistently more active than penicillin G or penicillin V as judged by the CD_{50} values when the antibiotics are given by the intramuscular route. No protection was obtained at doses of 100 mg. per Kg. when the penicillin resistant strain, *Staphylococcus aureus* 52-75, was used to infect, according to Gourevitch, Hunt, and Lein of Bristol Laboratories.

Potassium (alpha-phenoxyethyl) penicillin was studied pharmacologically and toxicologically in laboratory animals by Pindell, Tisch, and Hoekstra of Bristol Laboratories. This compound possesses no irritant liabilities when administered by intradermal, intramuscular, oral or even intrathoracic routes. No significant cardiovascular or autonomic effects were observed after intravenous administration of more than 200 mg./Kg. to dogs. No behavioral abnormalities or other signs of central nervous system involvement occurred after large single or multiple doses of the compound. Serum binding studies have demonstrated essentially similar protein affinities for potassium (alpha-phenoxyethyl) penicillin and potassium penicillin V. Serum disappearance curves in dogs given the new penicillin had essentially the same slope as those obtained with penicillin V indicating similar biological characteristics for the two compounds with regard to tissue distribution, excretion, and protein binding. The higher human blood levels attained with potassium (alpha-phenoxyethyl) penicillin in humans following oral administration therefore appears to be due to more efficient absorption of the new penicillin. Acute and chronic toxicity studies in rats and dogs have shown potassium (alpha-phenoxyethyl) penicillin to be no more toxic than potassium penicillins G and V. The intravenous $LD_{50's}$ of the new compound and potassium penicillin G in mice were 312 and 310 mg./Kg., respectively. Rats tolerated daily oral administration of 50 and 200 mg./Kg. for 7 weeks without alteration in growth rate, behavior, or histology. Dogs tolerated 200 mg./Kg. and 500 mg./Kg., p.o. similarly with no alterations in urinalyses, blood picture or biochemistry.

Approximately 10 subjects in a comparative study with potassium penicillin V were studied as to absorption and excretion. The peak serum concentrations with potassium

(alpha -phenoxyethyl) penicillin (3.46 ug./ml.) were approximately 2 fold higher than those of penicillin V (1.62 ug./ml.) and the penicillemia produced with potassium (alpha -phenoxyethyl) penicillin was essentially two times greater than with potassium penicillin V when measuring areas under the serum concentration curves (548 as compared to 292). Comparative urinary excretion studies with potassium (alpha-phenoxyethyl) penicillin and potassium penicillin V were carried out. Safety data on more than 3 weeks observations in 210 subjects was presented showing no adverse effects in hematopoietic, renal or hepatic functions. Forty-seven patients with infections caused by B. hemolytic streptococci and *S. aureus* organisms were treated with oral potassium (alpha-phenoxyethyl) penicillin. These clinical and laboratory studies were reported by Kligman, Morigi, Wheatley, and Albright of the University of Pennsylvania, Philadelphia, Pa. and Bristol Laboratories, Syracuse, N. Y.

Experiments were performed by Cronk, Naumann, Albright, and Wheatley of Syracuse University, Syracuse N. Y., to study the absorption and the rate of excretion in the urine of potassium (alpha-phenoxyethyl) penicillin following oral administration. All single-dose experiments were performed fasting. Serum samples were assayed for penicillin concentration at 0, ½, 1, 2, and 4 hours. Following 134 mg. doses (15 volunteers), the average serum concentrations were 0, 2.5, 2.2, 0.6, and 0.1 ug./ml., following 268 mg. doses (70 volunteers), they were 0, 3.6, 4.2, 1.3, and 0.09 ug./ml., and following 536 mg. doses (15 volunteers), they were 0, 7.3, 8.0, 2.7, and 0.02 ug./ml. The serum concentrations following 250 mg. doses of phenoxymethyl penicillin (25 volunteers) were 0, 3.2, 1.9, 0.6, and 0.1 ug./ml.

Ten volunteers received 536 mg. and ten received 268 mg. of the test antibiotic every 12 hours for 3 consecutive days. The first dose each day was given on a fasting stomach and the second was given approximately one hour after the evening meal. The average blood levels one hour after the morning doses of 536 mg. on the 3 days were 7.0, 7.2, and 8.3 ug./ml. and the average evening levels corresponding to the above were 5.4, 5.1, and 4.7 ug./ml. The average one-hour levels after the morning doses of 268 mg. were 4.7, 4.4, and 4.5 ug./ml. and the evening levels were 3.0, 1.6, and 2.7 ug./ml. Substantially higher blood levels are obtained in a fasting state. In these experiments, approximately 42-48 percent of the antibiotic was recovered in the urine during the first six hours and only 2-3 percent was recovered during the next six hours. Fourteen clinical infections have been treated successfully with potassium (alpha-phenoxyethyl) penicillin. These include pneumonia, ulceractive tonsillitis (hemolytic streptococcus), gonorrhea, ulcerative stomatitis, and cellulitis.

► POTASSIUM PHENOXYMETHYL PENICILLIN and the effect of ascorbic acid on its absorption were discussed by Herold, Hermansky, Smahel, and Vlcek of Antibiotics Research Institute, Roztoky near Prague. A number of substances was studied with the purpose of finding adjuvants enhancing the absorption of orally administered penicillin. Tablets containing 200,000 I.U. of procaine benzylpenicillin or phenoxymethyl penicillin (potassium salt or free acid) were administered together with the adjuvants in tablet or capsule form. Penicillin blood-plasma levels were determined 1,3,4 and 6 and (in some instances) 8 hours after administration. In screening the examined substances for adjuvant action, groups of 5 patients were used for each drug combination. Where positive results were noted, these were confirmed by cross-experiments using groups of 10 healthy volunteers (*i.e.* 20 absorption studies for each combination). Control groups of 5 patients or 10 volunteers, respectively, were used in each case.

Aminopyrine, which had been found to raise blood levels of orally administered benzylpenicillin, failled to do so with phenoxymethyl penicillin in either form. Citric acid lowered the blood levels slightly in most cases. Ascorbic acid, on the other hand, has proved remarkably effective with potassium phenoxymethyl penicillin, where simultaneous administration of 0.2 Gm. ascorbic acid doubled and 0.4 Gm. ascorbic acid trebled the penicillin level. Curiously enough, with the free acid of phenoxymethyl penicillin, no such effect was observed. The blood level curve proves an enhancing effect of ascorbic acid on the absorption of potassium phenoxymethyl penicillin, presuming that the plasma clearance value remains constant.

► SYNTHETIC PENICILLIN, dl-6-benzylsulfonamidopenicillanic acid (BzSP), is hydrolyzed by suspensions of penicillinase-producing staphylococci one half as rapidly as penicillin G. The residual material has no antibiotic activity. Apparently only one enantiomorph of the dl compound is biologically active. The rate of hydrolysis is linear until the reaction is at least two thirds complete. BzSP does not inhibit the rate of hydrolysis of penicillin G by staphylococcal penicillinase. BzSP stimulates an inducible increase in penicillinase in our test strain of staphylococcus. At low concentrations of antibiotic it is as effective as penicillin G, but when each compound is present in excess BzSP induces penicillinase to only 50 percent of the level achieved by penicillin G.

In tube dilution tests with small inocula the minimal inhibitory concentration (M.I.C.) of BzSP is 100 to 200 times as great as penicillin G against a penicillin-sensitive staphylococcus but only 4 to 10 times as great against the test strain of penicillinase producing staphylococcus. As the inoculation is increased the M.I.C. of BzSP rises more slowly than penicillin G, with the result that with large inocula (10^{-2} to 10^{-3} dilution of an overnight culture) the M.I.C. of BzSP is less than penicillin G. Mixtures of BzSP and penicillin G show no detectable synergism.

These results confirm that susceptibility to penicillinase may be appreciably lessened by chemical modification of the basic penicillin molecule albeit in this case at the expense of impairment of antibiotic activity. The decrease in susceptibility to penicillinase is accompanied by a diminution in the effect of inoculum size on M.I.C. Other derivatives with a more favorable combination of antibiotic activity and resistance to penicillinase may have more significant potential value against infection by penicillin resistant staphylococci, according to Cohen and Geronimus of Michael Reese Hospital, Chicago, and Beth Israel Hospital, Boston.

► POTASSIUM 6-(ALPHA-PHENOXYPROPIONAMIDE) PENICILLANATE was compared for *in vitro* effectiveness with penicillin G by Griffith, Ostrander, and Smith of the V.A. Hospital, Batavia, N.Y. Fifty-eight strains of *Streptococcus pyogenes* and fifteen strains of *Staphylococcus aureus* were studied. The streptococci consisted of 23 strains of Group "A," 12 of Group "B," 8 of Group "C" and 15 of Group "D." The staphylococci were from hospital patients with some obvious pathology. Minimum inhibitory concentrations were determined by conducting a parallel series of sensitivity tests for penicillin G and the synthetic penicillin (BL-P152). The sensitivities were conducted in a series of two-fold

dilutions of the antibiotic giving final concentrations from .097 units/ml. to 50 units/ml. All sensitivities were set up in heart infusion broth with 10 percent filtered sterilized human serum added. Seven strains of streptococci displayed some resistance to either penicillin G or BL-P152 beyond the .097 units/ml. level. The greatest resistance shown was to the 3.125 units/ml. level with no more than a 2-tube difference in the results of the two drugs. Two strains of staphylococci showed a two-tube difference with the two drugs. These results seem to indicate that the synthetic penicillin, BL-P152, is just as effective as penicillin G against streptococci and staphylococci plus the added pharmacological advantages.

► PENICILLINASE antiserum, though penetrating bacterial cells poorly, inhibits penicillinase *in vitro*. Simple compounds inhibiting penicillinase have been more encouraging *in vivo* but relatively weak. Therefore the effect of simultaneous use of antiserum on the potency of simple compounds inhibiting penicillinase was studied *in vitro* by Carr of the University of Michigan. Penicillinase effect was measured iodometrically after 30 minutes incubation in phosphate buffer (*p*H 6.5) at 30° C., using 40-400 units penicillinase (*B. cereus*), 0.0015-0.0048 M penicillin and controls. Rabbit antipenicillinase serum (1:450 dil.) gave 20-25 percent inhibition. Of 33 simple compounds (quinoline, sulfonamide, phenothiazine, thioamide and benzoate derivatives) screened at 10^{-3} to 10^{-5} M, none caused strong inhibition. At 10^{-1} M. benzoate derivatives were moderately active. Studying benzoate derivatives (10^{-1} M) and antiserum separately, a plot of penicillanase *vs* activity suggested reversible inhibition in each case. Combinations resulted in *antagonism* rather than addition or potentiation. Serum (studied alone *in vitro*) from 3 patients with recent penicillin-resistant staphylococcal infections did not inhibit penicillinase. Antiserum and the compounds studied both appeared reversible inhibitors. When combined they showed mutual antagonism, probably at least partly through non-specific interactions. Specific antagonism in part was also suggested.

► RIFOMYCIN is one of a group of antibiotics produced by *Streptomyces mediterranei n.sp.* and has now been named as rifomycin B. It is of interest because of its activity on gram-positive bacteria and mycobacteria and for its low toxicity. Rifomycin B is easily differentiated from the other components for its remarkable acidic character and good stability and for the higher solubility of its neutral salts according to Sensi, Greco, and Ballotta of Lepetit S.P.A., Milan, Italy.

Rifomycin B shows a degree of activity *in vitro* against gram-positive cocci at concentrations in the range of 0.01 to 0.5 ug./ml., the most sensitive microorganisms being *Streptococcus hemolyticus, Staphylococcus pyogenes aureus, Diplococcus pneumoniae*. Against gram-negative organisms rifomycin B is active only in a concentration of 1000 to 2000 ug./ml. and more. Mycobacteria are generally inhibited, particularly *Mycobacterium tuberculosis var. hominis*, which is sensitive to 0.05 ug./ml. The antibiotic is practically inactive against fungi. The influence of the inoculum size on the minimal inhibitory concentration has been investigated. Rifomycin B shows no cross-resistance when tested on microorganisms made resistant to the following antibiotics: penicillin, streptomycin, tetracycline, novobiocin, chloramphenicol, erythromycin, and oleandomycin. The ED_{50} protecting mice against the experimentally induced infection from *Streptococcus hemolyticus* and *Diplococcus pneumoniae* is 170 mg./Kg. and 190 mg./Kg. respectively. Although this dosage is somewhat high when compared with other antibiotics, the therapeutical ratio is still very favorable in view of the extremely low toxicity, according to Timbal of Lepetit S.P.A., Milan, Italy.

The pharmacologic properties of rifomycin B, a new antibiotic substance recently discovered, have been studied in mice, rats and dogs. Rifomycin B has a low toxicity and almost no side reactions. The intravenous LD_{50} in mice is 2040 mg./Kg. and in rats 1680 mg./Kg. By intraperitoneal and subcutaneous routes mice and rats tolerate doses as high as 2000 mg./Kg. Single daily subcutaneous 2000 mg./Kg. doses in rats for 20 days produce no significant changes in growth rate, in any element of the complete blood count and no pathologic alteration evident at gross and microscopic examination. Daily intramuscular 250 mg./Kg. doses of rifomycin B in dogs produce no deviation from normal in liver or kidney function test, blood clotting time, protein nitrogen levels, blood sugar levels and complete blood counts. Rifomycin B given in dogs and cats intravenously produces essentially no changes in blood pressure and respiration; only with doses higher than 100 mg./Kg. a slight hypotensive effect is noted. Rifomycin B does not modify the vasomotor action of epinephrine, acetylcholine or histamine or the effect of vagal stimulation upon the heart. Rifomycin B has no significant ganglioplegic, antispasmodic or anticonvulsant effect.

After subcutaneous injection of single 50, 25 and 10 mg./Kg. doses, appreciable blood levels are found in dogs for at least 5 hours. The antibiotic is found in unusual levels in the bile of dogs and rats. It has been determined that during the first 9 hours after intramuscular administration of 50 mg./Kg. doses a percentage of antibiotic from 50 to 65 percent is excreted with bile in dogs. Rifomycin B is poorly absorbed by oral route and produces a certain degree of local irritation after subcutaneous and intramuscular injection, according to a report by Maffii and Timbal, Lepetit S.P.A., Milan, Italy.

Studies on absorption and elimination were carried out by Furesz and Scotti, Lepetit S.P.A., Milan, Italy. By oral administration rifomycin B is not absorbed. Blood levels on 40 individuals were determined after parenteral administration. Two hours after a single intramuscular dose of 500 mg. and 1000 mg. of rifomycin B serum levels ranged between 1 and 5 ug./ml. and between 3.5 and 16.0 ug./ml. respectively. Six hours after the administration the serum levels were about 0.2 to 1-1.5 ug./ml. for both the doses administered. Only a small amount of parenterally introduced rifomycin B was eliminated by the urinary tract; the antibiotic passed through the liver and quantities of about several thousands ug./ml. could be detected in the bile. Rifomycin B passes in the ascitis fluid and in the milk, but did not pass through the healthy meninges.

Twenty-seven patients including both sexes and different age groups were treated with rifomycin B. The types of infection included: otitis media purulenta (4), dental abscess (20), furunculosis (2), proctitis, ulcerative colitis (1), mastitis or mammary abscess (5), fever of unknown origin (2), pulmonary abscess (3), chronic osteomyelitis (1), cholecystitis (3), gluteal abscess (3), and follicular tonsillitis (1). Dosage for the adult age group was 2 Gm. daily, given intramuscularly in two doses, and 30 mg./Kg. for children. Generally this treatment schedule was maintained for 4 to 6 days. The therapeutic effect of rifomycin B was definite and convincing. The majority of patients became afebrile within 24 to 72 hours and the local inflammatory and infiltrative processes showed a rapid regression. Only

in a few cases fever persisted and the treatment ought to be continued for a longer period but not exceeding 10 days. In the cases of pulmonary abscess the therapeutic effect was only transitory. The case of tonsillitis follicularis must be considered as "drug failure." No side reactions occurring during therapy were observed.

► RISTOCETIN, an antibiotic derivative of the actinomycete species *Nocardia lurida,* is effective clinically in a few special situations, primarily those involving systemic staphylococcal and enterococcal infections. The use of this drug may be attended with serious side effects involving principally the circulating blood platelets. These toxic reactions appear to be related to the dose of the drug rather than to individual sensitivity and are therefore preventable.

Eighteen patients were studied from a hemotological standpoint during and after ristocetin therapy in the past two years at the Walter Reed Army Hospital and Institute of Research by Gangarosa. Six of these patients developed significant platelet depression on large doses of the drug. *In vitro* studies exposing human and rabbit platelets to different concentrations of ristocetin, and animal experiments indicate that the site of the platelet destruction is in the circulating blood rather than on the bone marrow megakaryocytes. In pharmacological concentrations, ristocetin agglutinates red blood cells and denatures fibrinogen rendering blood incoagulable. When rabbits are challenged with large doses of this drug, an abortive form of intravascular coagulation takes place (the hemoclastic reaction of Crosby and Stefanini), probably due to the sudden release of platelet coagulation factors concomitant with lysis of platelets.

A clinical evaluation of ristocetin in children was presented by Asay, Dries, and Koch of Los Angeles Childrens Hospital. Ristocetin was given parenterally to 90 hospitalized children for 2 to 30 days. Fifty-seven of these patients had serious staphylococcic infections. Of the 90 children, 82 received intramuscular ristocetin. Eight patients received intravenous ristocetin only. Many of those receiving intramuscular ristocetin were treated with intravenous ristocetin until they were well enough to take fluids by mouth. Eighty-two of the patients showed a favorable response to this drug therapy. Clinical response was related to dosage with 50 mg./Kg./24 hours divided into three doses as optimum. Toxic reactions were generalized consisting of eosinophilia, neutropenia, and rash and localized consisting of thrombophlebitis, cellulitis, and one sterile abscess. Toxic reactions were closely related to dosage. Individual case reports demonstrate the inability of ristocetin to cross even the inflamed meninges or to penetrate into abscess cavities.

Methods for the commercial production of crystalline ristocetin A sulfate and other salts and base were presented by Stainbrook, Cardinal, and Clark of Abbott Laboratories. While the original material was an outstanding success therapeutically, it showed some minor side effects, which declined markedly during the later months of the first year of ristocetin usage. One of the possible explanations was the introduction of crystalline ristocetin A sulfate, prepared by a process that was developed at Abbott Laboratories. The process involved adsorption on a resin followed by an elution. The ristocetin A sulfate was then crystallized and the crude crystals isolated. Ristocetin B and some of the impurities are removed in this step. The crude crystals are redissolved in water-acetone, and carbon-treated to remove colored impurities and pyrogens. The purified ristocetin A crystals are recovered and dried.

► SPIRAMYCIN and procaine penicillin were used in the treatment of scarlet fever by Skalmowski and Jeljaszewicz of Poznan State Hospital and Medical Academy, Poznan, Poland. Eighty-four children with scarlet fever were hospitalized one or two days after the outbreak of illness. The patients were divided into three groups: one received penicillin for 10 days intramuscularly; the second, spiramycin for 10 days; and the third was untreated. In all children smears from nose and throat were seeded on the Pike's broth and blood agar on the 1, 2, 3, 4, 5, 10, and 20 day of the illness. At the same time antistreptolysin 0 and the C-reactive protein were detected. With spiramycin and penicillin, equally satisfactory results were obtained, both from the clinical and bacteriological point of view. Spiramycin, however, controlled better the complications occurring during the period of hospitalization.

► STAPH INFECTIONS and bacteriological studies of clean surgical wounds and the personnel of an 800-bed hospital were discussed by Wright, Weinstein, Reedy, Oswald, and Pocurull of the Food and Drug Administration, and The Washington Hospital Center, Washington, D.C. The relationship between the bacteriology of surgical incisions and the development of postoperative infection was studied. Over 1,000 clean surgical incisions were cultured in the operating room prior to closure. No organisms were recovered from 772 cases (76%). The remaining 248 cases yielded 346 cultures, 270 of which were gram-positive cocci. Only 20 coagulase-positive staphylococci were detected. All organisms were tested for antibiotic susceptibility and coagulase-positive staphylococci phage-typed. Eight postoperative infections developed (0.8%). Four yielded coagulase-positive staphylococci of phage type 80/81/82 resistant to penicillin, streptomycin, and the tetracyclines, one yielded a coagulase-negative staphylococcus, one a diphtheroid and one a coli. No growth was obtained from culture of one of the postoperative infections. In one case only was a coagulase-positive staphylococcus phage type 80/81/82 recovered from the surgical incision and from the postoperative infection that developed.

To locate hospital sources of staphylococci, nasal swabs were taken from 101 of the surgical staff and 152 of the ward nursing staff. Coagulase-positive staphylococci were found in 22 of the former group (22%) and 40 of the latter group (26%). Strains of phage type 80/81/82 occurred in 4 of the surgical and 15 of the nursing staff. Of the 14 operations which yielded coagulase-positive staphylococci, 12 were attended by personnel tested for nasal staphylococci and 8 of these by personnel from whom coagulase-positive staphylococci were recovered. In 4 instances it appeared that the incision culture and the nasal culture of a staff member present at the operation were probably identical. In all 4 of the postoperative infections caused by type 80/81/82 staphylococci, the same type was carried by one or more of the nurses on each patient's ward.

A nine year study of coagulase-positive staphylococci in a burn unit—incidence, resistance pattern, carriers, and phage typing—was reported by Haynes, Jones, and Gibson of the Medical College of Virginia, Richmond, and Tufts University School of Medicine, Boston. During the period 1951-1959, 3,641 wound cultures were performed, and 1937 contained coagulase-positive staphylococci. The percent of patients demonstrating this organism has increased progressively during this period, as has the percent of wound cultures. Resistance appears to be related to usage; however, a pattern of variable resistance is suggested, dependent upon drug type, and independent of usage. Bacitracin has

maintained its almost complete effectiveness in spite of considerable local usage. Chloramphenicol, though used considerably more than erythromycin, has maintained approximately the same effectiveness (approx. 40%). Penicillin, streptomycin and tetracycline have approached 100 percent *ineffectiveness* with usage. A combination of bacitracin, neomycin, and polymixin (BANEPO) applied locally to burn wounds has not been effective in removing staphylococci though significant resistance did not develop to these agents.

► STREPTONIGRIN has been isolated from the culture filtrates of *Streptomyces flocculus*. It is a new crystalline antibiotic with antitumor properties. For isolation, the broth is acidified and extracted with solvents such as n-butanol or ethyl acetate. The extract is concentrated and, after preliminary purification, subjected to counter-current distribution in the system 3 percent phosphate buffer (*p*H 7.5) and ethyl acetate. The major active component accumulated in approximately the center of the distribution. It is recovered and crystallized first from ethyl acetate and then from acetone. Streptonigrin separates out as dark brown rectangular plates which melt at 275° C. with decomposition. Its elemental analysis indicates an empirical formula of $C_{24}H_{20}O_8N_4$. It behaves as an acidic compound with quinonoid properties. Streptonigrin is active against many gram-positive and gram-negative bacteria. It shows a high degree of activity against Adenocarcinoma 755 and human tumor HS#1 transplants grown in rats and only a moderate activity against Sarcoma 180 and Leukemia 1210. This report was presented by Rao and Cullen of the John L. Smith Memorial for Cancer Research Maywood, New Jersey.

► STREPTOVITACINS A, B, C_2, and D and their antitumor activity were discussed by Evans, Ceru, and Mengel of The Upjohn Comany. The *in vivo* antitumor activity of streptovitacins A, B, C_2, and D and the related compound cycloheximide were compared. The tumors were Walker 256, Sarcoma 180, and Ehrlich carcinoma (ascites). Streptovitacins A and D are equivalent in activity when tested against Walker 256 and are more active than cycloheximide. Streptovitacin A was found to be 70 to 100 times more active than B and C_2 when tested against Walker 256, Sarcoma 180, or Ehrlich carcinoma (ascites). The relative *in vivo* activity of the streptovitacins agreed well with *in vitro* cytotoxic activity reported by Smith (Cancer Research, in press) against KB cells.

► STREPTOZOTOCIN is an antibiotic produced by *Streptomyces achromogenes* var. 128. It is unstable at neutral and alkaline conditions. Streptozotocin shows activity against a variety of both gram-positive and gram-negative organisms. It is not cross-resistant with novobiocin, carbomycin, celesticetin, chloramphenicol, erythromycin, kanamycin, penicillin, polymyxin, and tetracycline. Paper chromatography shows that streptozotocin is a new antibiotic, according to Vavra, DeBoer, Dietz, Hanka, and Sokolski of The Upjohn Company.

Herr, Eble, Bergy, and Jahnke of Upjohn demonstrated that crystalline streptozotocin is a water-soluble material with an apparent empirical formula $C_{11}H_{21}N_3O_{12}$. Chemical studies have shown the presence of an N-nitroso group, probaly as an N-nitrosomethylamide group.

The *in vitro* and *in vivo* (mouse) antimicrobial activity of streptozotocin was described by Lewis and Barbiers of The Upjohn Company. *In vitro*, it was active against numerous pathogenic bacteria, including streptococci, staphylococci, diplococci, enterococci, coliforms, *Pasteurellae*, *Salmonellae* and *Proteus* species. *In vivo*, streptozotocin compared favorably with other commonly used antibiotics in protecting mice infected with *S. aureus*, *S. hemolyticus*, *S. viridans*, *D. pneumoniae*, *P. multocida*, *P. vulgaris*, *S. paratyphi B*, *S. typhimurium* and *K. pneumoniae*. The antibiotic was active over a wide hydrogen-ion range but was most active in acid media. Neither serum nor urine interfered with the antibiotic's *in vitro* activity. There was no evidence of cross-resistance between streptozotocin and other antibiotics when tested against resistant strains isolated from hospital patients and organisms made resistant in the laboratory. Induced resistance to streptozotocin was of the streptomycin type.

Bacterial resistance to streptozotocin was reported by Hanka, Sokolski, and Vavra of The Upjohn Company. Studies were made with two stains of *Staphylococcus aureus* and one strain of *Proteus vulgaris*. Resistant mutants were isolated from both species following the first contact with the antibiotic when an inoculum of sufficient size was used. Naturally resistant mutations occurred at the rate of one in 10^5 - 10^6 sensitive cells in a 24-hour culture. Streptomycin-like resistance development was observed in both strains of *Staphylococcus* whereas gradual buildup appeared to be the prevailing pattern with *P. vulgaris*. In both strains of *Staphylococcus*, resistance to streptozotocin was retained tenaciously. After 50 consecutive transfers in the absence of the drug almost the whole population was still resistant.

Streptozotocin was not cross-resistant with novobiocin, celesticetin, chloramphenicol, erythromycin, kanamycin, neomycin, penicillin, polymyxin, or tetracycline. Limited study on the physiological background of the bacterial resistance to streptozotocin showed that such resistance was not due to the ability of resistant cells to destroy the drug.

► SULFONAMIDES in the treatment of tuberculosis were discussed by Weiss, Eisenberg and Flippin of Philadelphia General Hospital. Some early studies of the sulfonamides showed that many of them were tuberculostatic *in vitro* and had demonstrable effects in guinea pig experimental tuberculosis. This information seems to have been neglected until interest in the use of sulfonamides for combined therapy of tuberculosis arose recently in Japan. The authors investigated the *in vitro* potency of three sulfonamides against tubercle bacilli. Sulfasoxizole and sulfadimethoxine were found to be tuberculostatic at concentrations of 20-50 ug./ml. Sulfaethylthiadiazole was not so effective. On the basis of these studies the authors have begun a controlled clinical study to compare INH-sulfadimethoxine with INH-PAS as to therapeutic efficacy and the emergence of bacterial resistance in advanced original treatment cases of tuberculosis.

Comparative clinical evaluation of sulfaphenazole, sulfadimethoxine and sulfamethoxypyridazine was reported by Frisk and Holmgard of the Medical Service of Ersta Hospital and Central Laboratory S:t Erik's Hospital, Stockholm, Sweden. The blood concentration and urinary excretion of sulfaphenazole, sulfadimethoxine and sulfamethoxypyridazine were followed after single 4 Gm. doses of the drug. To each of three persons on different occasions the 3 compounds were administered. In another group of persons (comprising 15 subjects for each drug) the blood concentration of the various drugs during continuous treatment was followed. In another group of patients the renal clearance was determined simultaneously with creatinine clearance. The amount of the drugs bound to the serum protein was also assayed. All three drugs are absorbed rapidly, completely and the renal elimination of the compounds takes place slowly. Sulfamethoxypyridazine gives the highest and most long lasting blood concentration. That of sulfadimethoxine is somewhat lower and that of sulfaphenazole the lowest.

The degree of acetylation of all drugs is small. The renal clearance of sulfamethozypyridazine and sulfadimethoxine is about equal and two to three times lower than that of sulfaphenazole. All drugs are to a high and about the same extent bound to the serum proteins. All the drugs were well tolerated and no toxic reactions in the blood or kidneys have been demonstrated. The chemotherapeutic activity of the drugs seems to be the same.

► TETRACYCLINES. The relative merits of the 4 tetracylines were discussed by Garrod and Waterworth of St. Bartholomew's Hospital, London. There are slight differences in the antibacterial activity of tetracycline and chlor- and oxytetracycline *in vitro*. An accurate comparison with numerous strains shows, *e.g.*, that chlortetracycline has greater activity against staphylococci and pneumococci. There are also said to be differences in their tendency to cause diarrhea. This question has been examined by analyzing data from the charts of 288 patients treated with tetracyclines for pneumonia who, in 8 days, had a total of 2,606 bowel actions. Differences in the frequencies of diarrhea are remarkably slight and although they favor tetracycline, the average dose of this drug given was lower. Demethylchlortetracycline (DMCT) is reported to produce higher blood levels, dose for dose, than tetracycline, owing to slower excretion. Its capacity to inhibit the growth of 12 species of bacteria *in vitro* has been examined; it exceeds that of tetracycline by two-fold for most or all strains of 8 of them. Serial viable counts of staphylococci exposed to low concentrations of chlortetracycline and DMCT show the same rate of death for both antibiotics, succeeded by growth when chlortetracycline has lost its activity, whereas in the presence of DMCT the count falls to nil. DMCT may therefore be regarded as chlortetracycline with the added advantage of stability.

The tetracyclines in amebiasis was the subject of a paper by Elsdon-Dew of the Amoebiasis Research Unit, Durban, South Africa. Over 300 cases of acute dysentery have been given various tetracyclines, in differing dosages, singly and in combination with other drugs, and results were compared and contrasted with other forms of therapy. The choice of cases for trial therapy was strict and the assessment was based not only on the disappearanec of parasites but also on the sigmoidoscopic appearance from day to day. As single drugs, some forms of tetracycline are unequalled in the treatment of the acute condition, but the occurrence of relapses and of liver abscess indicates the necessity for adjuvant therapy. With the use of quinolines, smaller doses of tetracycline may give similarly good results, with protection against complications. Demethylchlortetracycline, is shown to be relatively ineffective.

► TETRACYCLINE and tetracycline plus 6 methylprednisolone were used in a controlled blind study to evaluate their effects on the clinical course of pneumococcal pneumonia. The tetracycline and the tetracycline-steroid capsules were identical in appearance and given under a code number. The identity of the capsules was unknown until the end of the study. Both groups of patients received 2 Gm. of tetracycline per day, 500 mg. every 6 hours by mouth for a minimum of 5 days or until they were afebrile for a period of 48 hours. Those patients receiving steriods were given a total of 32 mg. of 6-methylprednisolone on the first day, 16 mg. the second and third days, and 8 mg. on the fourth day. The 6-methylprednisolone was given in divided doses in the same capsule as the tetracycline. The study was carried out over a 2-year period and there was a total of 42 patients, 21 in each group. The patients were analyzed in relation to their clinical response and resolution of the pneumonia by x-ray.

In the tetracycline series, 7 patients (33.3%) were afebrile 24 hours after therapy was initiated as compared to 13 patients (72.2%) in the tetracycline-steroid group. In the tetracycline-steroid group, there was a more rapid clinical response than in those patients treated with tetracycline alone. Except for the adverse course in one patient, a more rapid improvement in the clinical course was noted in the tetracycline-steriod group, according to Kirby, Polis, and Romansky of George Washington University School of Medicine and D. C. General Hospital Washington, D. C,

The effect of long-term tetracycline therapy on chronic bronchitis was studied by Norman, Hook, Petersdorf, Cluff, Godfrey, Ribble, and Levy of The Johns Hopkins Hospital, Baltimore. Using a double blind technique patients were given 1 Gm. of tetracycline a day or placebos for a 3 month period, following which the alternate drug was given for a second 3 months. Thirty patients were observed for 78 treatment periods divided equally among tetracycline and placebo. The results of therapy were as follows:

	Placebo	Tetracycline
Better	11	21
No change	15	11
Worse	13	7

A total of 33 gonococcal infections in 31 male patients have been treated by Laird at St. Luke's Clinic, Manchester, England, using two dosage schedules: 20 infections were treated with a single, intramuscular injection of tetracycline phosphate (equivalent to 250 mg. tetracycline hydrochloride) and a further 13 patients received one injection on two consecutive days. Clinical cure took place in 75 percent of patients receiving one injection and 92 percent of those given two injections. It was concluded that injectable tetracycline phosphate complex, in a dosage equivalent to 250 mg. of tetracycline hydrochloride daily for not less than 2 days, is an effective treatment for gonorrhea in the male. Penicillin therapy remains the treatment of choice but injectable tetracycline phosphate would be a suitable alternative in penicillin-resistant cases.

► N-PYRROLIDINOMETHYL TETRACYCLINE for parenteral use was discussed by Kaplan, Albright, and Buckwalter of Bristol Laboratories, Inc. Serum concentrations in man, following intramuscular injection are given with single doses of 350 mg. of N-(pyrrolidinomethyl) tetracycline and with three multiple dose regimens of 350 mg. of N-(pyrrolidinomethyl) tetracycline. The serum concentrations after a single dose range from 5.63 ug./ml. at one hour to 0.79 ug./ml. at 24 hours. The regimen of 350 mg. every 24 hours gave peak serum concentrations of 5.36 ug./ml. to 6.41 ug./ml. and trough serum concentrations of 0.60 mcg./ml. to 1.23 ug./ml. Serum concentrations in man, following intravenous injection, are reported with single doses of 350 mg. and 700 mg. of N-(pyrrolidinomethyl) tetracycline using several dosage schedules. The results obtained suggest that N-(pyrrolidinomethyl) tetracycline is more than 70 percent more efficiently absorbed than is tetracycline hydrochloride and tetracycline phosphate complex. Single daily intragluteal injections of 350 mg. of N-(pyrrolidinomethyl) tetracycline give serum concentrations that should be adequate for the treatment of most susceptible infections.

Treatment of 1,200 patients with repeated intravenous doses of pyrrolidinomethyl tetracycline was reported by Koch of the University of Giessen, Giessen, West Germany.

The drug has been used since 1957 and technically it is easier to administer than other injectable tetracyclines (250 mg. dissolved in 10 ml. can be given intravenously within 1 minute). In this study 1,200 patients were treated: 286 for pneumonia, bronchiectasis, lung abscess; 348 for acute and chronic pyelonephritis; 118 for various infectious diseases (brucellosis, meningitis, endocarditis); 56 for cystic pancreas fibrosis with lung affection; 88 for agranulocytosis, radiation neutropenia, leukemia; 286 for antibacterial protection during corticoid treatment; and 62 prophylactically after tonsillectomies and teeth extractions. Treatment consisted of: single dose: 250 mg. q.d., occasionally 250 mg. b.i.d. Total dose: 0.5-20.0 Gm. In contrast to the oral therapy prompt results were obtained and rapid decrease in temperature. Lung abscesses, which were resistant to tetracycline hydrochloride previously were cured. Lowering effect was noted upon the previously fixed pyelonephritic hypertension in one third of the cases. Side effects included taste sensation during the injection for 1 minute only. No allergy, toxicity, soft stools, enterocolitis, or nausea were seen. Pyrrolidinomethyl tetracycline intravenously as standard antibiotic therapy is superior to any other tetracycline preparation, because of the fast onset of action and absence of side effects.

Use of injectable tetracycline preparations in gonorrhea was reported by Willcox of St. Mary's Hospital, London. Of 20 patients so far given single injections of 250 mg. of pyrrolidinomethyl tetracycline, 15 have been followed and there have ben 2 failures (13.3 percent of those followed). The effectiveness of only 250 mg. of this preparation was thus similar to that of 500 mg. of tetracycline phosphate. Moreover, pyrrolidinomethyl tetracycline proved much better tolerated locally.

► TETRAZOLIUM SALTS are reduced by actively metabolizing cells and are converted to colored insoluble formazans in the cytoplasm. Five of these compounds, triphenyl tetrazolium chloride (TTC), neotetrazolium (NT), blue tetrazolium (BT), iodo-nitro tetrazolium (INT) and nitro blue tetrazolium (NBT) were tested for their effect on seven bacterial species: *Escherichia coli, Salmonella typhimurium, Proteus vulgaris, Shigella sonnei, Staphylococcus aureus, Streptococcus pyogenes,* and *Bacillus subtilis.* The minimal inhibitory dose (MID) as well as the comparative reduction rates were determined. Previous studies with neotetrazolium had shown that gram-positive organisms have a lower MID and are more susceptible to the lethal effects of this compound than gram-negative organisms (Antopol, Glaubach and Goldman, Pub. Health Repts., *63,* 38, 9/48.,p.4). The present study showed similar effects with all tetrazolium salts tested. A rapid reduction rate and a more intense formazan production were observed with gram-negative organisms. Proteus cultures reduced all the tetrazolium salts faster than did the other species investigated, maximal reduction occurring usually within two hours. For NBT, the most effective of the tetrazolium salts, the MID ranged from less than 2 mcg./ml. for *Streptococcus pyogenes* to 125 mcg./ml. for *Escherichia coli.* The decreasing order of inhibitory effectiveness of the salts was NBT, NT, BT, INT and TTC, according to studies by May, Winter, and Antopol of Beth Israel Hospital, New York.

► TRIACETYLOLEANDOMYCIN was studied by Werthamer of the Paul Kimball Hospital, Lakewood, New Jersey. About 100 patients were treated for upper respiratory and cutaneous infections. The series included staphylococcus nasal carriers. Patients ranged in age from one month to over 70 years of age (about ⅓ were children) and the dosage schedule ranged from 40 mg. per Kg. per day to 500 mg. 4 times daily. Triacetyloleandomycin was extremely effective in approximately 85 percent of all acute infectious diseases encountered. Of 31 cases of staphylococcal phage type 80/81 infections, it was completely effective in 27 cases. No resistance was encountered. There was excellent correlation between the *in vitro* sensitivity and *in vivo* effects. Few side effects (approximately 6 percent) were encountered. Seven cases responded effectively following failure with penicillin. Three of four nasal staphylococcal phage typed 80/81 carriers were reverted to negative carriers through use of triacetyloleandomycin.

Carroll, Gibas and Karellos of the St. Louis University School of Medicine, St. Louis, Missouri, reported on the use of triacetyloleandomycin with triple sulfas in urological infections. This study included over 500 patients with prostatitis, urethrocystitis, and pyonephritis; paraplegic patients with indwelling catheters; surgical patients, and pediatric urological infections. Results indicate that combination of triacetyloleandomycin with triple sulfa has a distinct place in combating the spread of resistant cocci. Only six patients in this series had side reactions, none of which were serious. Three developed skin rash, two developed gastrointestinal disorders requiring the discontinuance of the drug, and one developed headache. The drug combination was compared with placebos in one series of patients.

After studying triacetyloleandomycin therapy of infections caused by certain gram-positive bacteria or *Klebsiella,* Kraljevic of The Ramon Barros Luce Hospital for Contagious Disease, Santiago, Chile, concluded that the drug is a valuable contribution to clinical therapy, particularly since it is effective against Klebsiella infections and can also overcome infections caused by staphylococci resistant to other chemotherapeutic agents.

Reporting experiences with triacetyloleandomycin in a rheumatic fever prophylaxis clinic, Mou of the State University of New York Medical College, Syracuse, concluded that while penicillin remains the drug of choice for oral streptococcal prophylaxis, triacetyloleandomycin would appear to be worthy of further trial in those patients who are allergic to penicillin.

Warenbourg of the University of Lille, France, observed that triacetyloleandomycin is apparently an excellent agent for the treatment of bacterial infections of the respiratory tract particularly those that have proved resistant to some of the other currently employed antibiotics.

Olansky and McCormick, Jr. of Duke University Medical Center, Durham, North Carolina, used triacetyloleandomycin alone in 41 of 60 pustular acne cases, and in 16 of 32 cases with cystic lesions. This antibiotic plus a vaccine (*Corynebacterium acnes* and *Staph. albus* grown anaerobically) were used in the other 19 pustular and 16 cystic cases. Triacetyloleandomycin controlled the pustular phase very well. Desensitization with vaccine served to influence the type of relapsing lesions months later—they were smaller, and showed very little induration and cyst formation. In the 59 pyodermas treated with triacetyloleandomycin, 48 showed an excellent response, 10 a good response, and one a fair result. Side effects were minor and bacterial resistance was not observed.

Eskelson of the University of Utah Medical School, Salt Lake City, compared triacetyloleandomycin with oleandomycin. Bacterial cultures were obtained on all patients and the bacteria identified and sensitivity tests performed. One hundred and seventy cases of acne were placed on these drugs, 250 mg. four times daily for 4 to 8 weeks. Adjunctive therapy was continued in most cases. Eighty-one

percent of the patients on triacetyloleandomycin had excellent or good therapeutic results. Sixty-four percent of the patients administered oleandomycin had excellent or good therapeutic results. Follow up revealed recurrences of acne in many instances when the drug was stopped. The authors conclude that triacetyloleandomycin is an important addition to the therapeutic regimen of pustular and cystic acne, but older therapeutic measures are required to hold the gains attained by the antibiotic.

Nebulizations with the combination oleandomycin-tetracycline in the treatment of acute or chronic bronchitis in children were discussed by Albores, Weinstein and de la Plaza of Policlinico Lanus, Argentina. Daily nebulizations were made using 50 mg. of the combination for the younger children and 100 mg. for the older ones. Duration of treatment ranged from three to twelve days. No germs, or resistant strains to the combination oleandomycin-tetracycline were found. Forty cases responded satisfactorily (80%); six cases were fair (12%), and 4 cases did not respond (8%). There were no side effects and the treatment was very well tolerated, with the exception of two children who developed a light skin rash.

► TRICHLORPHENOXY PROPIONIC ACID and the potentiation of antibiotics in the treatment of experimental infections was the subject of a study by Scherr, Nelson, and Gerencser of The University of Illinois, College of Medicine, Chicago.

Experiments with mice infected with *K. pneumoniae* and treated with streptomycin indicated that the protective effect of the streptomycin, as manifest by surviving mice, could be markedly enhanced by a potentiating action of 1-(2,4,5-trichlorophenoxy) propionic acid given concomitantly with the streptomycin. The potentiating agent when used alone had no protective effect on infected animals. A similar but less vivid potentiating effect was found when 2,4,6-trichlorophenol was used with the streptomycin. Animals infected with a beta-hemolytic Group A *Streptococcus* and treated with a mixture of penicillin and 1-(2,4,5-trichlorophenoxy) propionic acid showed survival data which were twice as great as animals treated solely with the penicillin. These experiments are an extension and confirmation of extensive *in vitro* studies with potentiators of antibiotics and suggest their possible clinical use especially in the light of their low toxicity.

► VANCOMYCIN in the therapy of staphylococcal endocarditis was discussed by Geraci and Heilman of the Mayo Clinic and Mayo Foundation, Rochester, Minn. Sixteen patients who had had staphylococcal endocarditis less than 6 weeks were treated with vancomycin. Fifteen organisms were coagulase-positive and one was coagulase-negative. Sources of infections were: ulcerative lesions of the skin, five patients; instrumentation of urinary tract, one; postoperative infections, four (two cardiac, one prostatic, one abdominal); and no demonstrable source, six. All organisms were inhibited by 3.12 ug. of vancomycin or less per milliliter. Minimal concentrations needed to kill the organisms in serum were the same. Therapy with vancomycin lasted from 2 to 4 weeks (2 weeks, three patients; 2½ weeks, two; 3 weeks, five; 4 weeks, two; 2½ to 9 days, four). A dose of 0.5 or 1 Gm. was given slowly intravenously every 6 or 12 hours over a 4-minute period. Infection was eliminated in 11 (70 percent); eight deaths occurred (50 percent), with infection controlled in three patients and uncontrolled in five. Death resulted from congestive heart failure, from severe progressive toxemia due to active infection, or from both, before adequate therapy could be given in some cases. Two-gram daily doses of vancomycin give a good killing effect in the patient's serum as determined by serum bactericidal tests (performed in 15 of 16 patients). The dilutions of serum giving a total killing effect varied from 1:4 to 1:16, almost always being 1:8. Toxicity from vancomycin was minimal, manifested mostly by variable phlebitis. Vancomycin is an effective bactericidal agent in the therapy of staphylococcal endocarditis.

The use of vancomycin in the prevention of infection in surgical wounds was discussed by Carson and Finneran of Indianapolis, Ind. The authors gave vancomycin intravenously during the performance of all thoracic operations and followed with another injection the following day. Vancomycin was chosen because it had demonstrated the power to kill Staph. organisms directly rather than act as a bacteriostatic agent. In addition there was evidence that Staph. organisms did not develop a resistance to this new drug. They used vancomycin in 114 cases without a serious infection or evidence of serious reaction during or following the administration of this antibiotic. The ages of the patients range between 2 and 76 years and there were many attendant degenerative changes in the older patients.

Use of vancomycin in pediatrics was reported by Spears and Koch of Los Angeles Childrens Hospital. Based upon the analysis of 54 serum vancomycin samples gathered for this report, the recommended dosage for children should be 40 mg. per Kilo per day administered intravenously. Continuous infusion technique is preferred. Vancomycin did not diffuse into the cerebrospinal fluid in detectable amounts. Vancomycin was given as a therapeutic agent to 23 patients extremely ill with various staphylococcal infections. Sixty percent responded with cure or improvement, 18 percent were unimproved and 20 percent expired. It is the authors impression that vancomycin is an excellent antibiotic for the treatment of seriously ill patients with staphylococcal infections that have failed to respond to other antibiotics. Although the incidence of side reactions was high, no severe toxic manifestations were noted with the possible exception of an infant who expired shortly after receiving a rapid intravenous drip of vancomycin.

Treatment of severe staphylococcal infections in infancy and childhood with vancomycin was discussed by Riley and Ryan of the University of Oklahoma Medical Center, Oklahoma City. Twenty-four infants and children with serious staphylococcal infections were treated with vancomycin. The age of the patients ranged from 2 weeks to 15 years. Included in the group were 8 patients with septicemia, 6 with pneumonia, 2 with bacterial endocarditis, 2 with osteomyelitis, 4 with extensive cellulitis and skin abscesses, and 2 patients with severe periorbital cellulitis. Several patients exhibited multiple clinical manifestations of staphylococcal disease. All patients were considered to have severe staphylococcal infections and many had been treated previously with other antimicrobial agents unsuccessfully.

Appropriate pre- and post-treatment cultural data and pertinent studies referable to toxicity were obtained. Dosage ranged from 12.5 to 100 mg. per Kg. per day and the duration of therapy by the intravenous route varied considerably depending on the nature of the individual disease process and response. The most common untoward reactions were localized chemical phlebitis at the site of the injection and an occasional febrile response to the drug. The latter was significant in certain cases since it made evaluation of therapeutic response difficult. There was no evidence of persistent renal or auditory impairment. The results in the treatment of staphylococcal infections were generally good, especially in view of the critical nature of the infections.

THE PHARMACY STAFF CONFERENCE

by WILLIAM E. DUDLEY

Men are never so likely to settle a question rightly as when they discuss it freely.
LORD MACAULAY, 1830

► AS A MEDIUM OF COMMUNICATION MAN HAS accepted the conference as a segment of his way of life. He trusts vital decisions affecting his well-being to the conference; he conducts business by conference; and his government utilizes the conference to make and change the law. Indeed, as an instrument of achievement, the conference today overbalances oratory.

The conference approach can be put to use in teaching and problem adjustments within the pharmacy service. This same pattern is utilized in journal abstracts, progress reports on assignments, pharmacology reviews, etc. The number and diversity of topics can justify a pharmacy staff conference on a weekly basis.

To institute the weekly pharmacy conference, the chief pharmacist prepares several items of agenda and assigns the topics to the staff members. The hour to be set aside can be determined by the chief pharmacist. The first hour of a suitable day might be appropriate. Notification of the meeting is sent to the other services within the hospital. All staff pharmacists take part in the conference. The pharmacy helper, clerk, and other nonprofessional employees do not participate.

The conference should not exceed one hour. A room adjacent to the pharmacy with a telephone is advantageous. The room should be well lighted and well ventilated. The conference members sit at a rectangular table without a prearranged seating plan. A blackboard is a convenient addition.

The following is a typical agendum for such a conference:

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1. Announcements and assignments (5 min.).
2. Pharmacology Review—The Vermifuges in the *American Hospital Formulary Service*—by E.E.M., Staff Pharmacist (20 min.).
3. Progress Report—Sterility tests on a group of ophthalmic preparations—by the Intern (10 min.).
4. Discussion Period—Problems and policies as found in the Outpatient Dispensing Area—Discussion Leader—P.K.H. (20 min.).
5. Comments and critique.

Agenda are prepared two weeks in advance of the conference. To stimulate initiative, journal reports and pharmacology reviews are assigned without comment as to content. Minutes of the conference are prepared in brief outline only. The leadership of the discussion period is rotated among the members.

Discussion Period

The discussion period is one of the more spirited components of the staff conference. The subject for discussion and the discussion leader are selected in advance. Each participant enters the session with an "open mind" and ready to accept new ideas and new methods. Incomplete discussions and the introduction of personalities should be avoided.

Fansler* calls good listening the number one role of human relations. This may be forceful, but good communication is certainly close to the number one role, and that implies two way traffic: clear talking and good listening.

The Discussion Leader

The discussion leader states the problem briefly, keeping it within narrow channels. It is his responsibility to return the group to the subject when the discussion strays or widens into generalities. In this capacity he assists as a catalyzer. The democratic-permissive type of leader is most effectual. He does not impel the members around but feels as a member, learning as they learn. He keeps the members from wandering too far from the topic, and foresees ensuing trouble.

*"Creative Power Through Discussion" by Thomas Fansler, Harper & Bros., N.Y.

To avoid even the semblance of autocracy, the leader uses questions rather than statements. "I wonder whether we have quite covered the time factor of the procedure?" is better than "The most important point, the time factor of the procedure, has not been mentioned."

The most grievous mistake the discussion leader can make is to use ridicule. No matter how wrong the member seems to be, to ridicule him will normally cause the participants to group up solidly against the leader.

The leader should watch closely for approaching conflict; an increase in formal politeness is one sign, "Mister Jones" instead of "Ralph." Other signs are, switching from an opinion to a person; a member folding his arms with some ostentation.

Incipient controversies may often be quenched with facts. It is difficult to start a quarrel on a factual level, but it will burn like dry grass on the opinion level. A sharp word or two introduced by the leader may prevent a flare-up and a possible explosion.

At intervals, the leader should introduce a "feed back" - "Let's see where we are? Could we summarize the discussion so far like this?" or "Are we agreed on these principle points?" The periodical recall keeps the group on the subject and tends to discourage irrelevant contributions. The leader's use of a blackboard is particularly useful for summarizing.

All Group Members

Never sit down with your mind made up. Something really new may come out of the discussion.

"We think" is better than "I think" or "It is my opinion."

Make a real effort to employ most of your time to the art of good listening.

Sit down wtih the expectation that every member will contribute something of importance out of the wealth of his own experience. Expect it to be as important as anything you might have to contribute.

Experience has shown that consensus is better than voting. A vote immediately operates to split the group into winners and losers.

The minority view, even when it is impractical, has a right to be expressed. This right of expression is important in the broader picture. Minority opinions often turn out to be good ideas when time is taken to examine them closely.

The discussion period may be productive in:

1. Solving problems where group judgment is superior to individual decision.
2. Making decisions subsequent to fact finding and study.
3. In the interpretation of new methods and skills.
4. In the re-evaluation of procedures.

Agenda Topics

The following is a list of possible agenda topics for the Weekly Pharmacy Staff Conference.

Standardization of stock labels

The newer diuretics—mode of action and dosage

The selection of preservatives for ophthalmic solutions

Delegation of authority

Interesting abstracts from journals

Observations made on a recent visit to a manufacturing plant

Investigational drugs

Time saving devices

A review of the antihypertensive drugs

Basic chemistry of the steroids

Accreditation points in hospital pharmacy

Lotion formulation

Supervisory potentials

Improving the method of handling inquiries on the phone

Inter-departmental relationships

Budgetary problems

A review of the duties of the pharmacy helper

Functions of the Pharmacy and Therapeutics Committee

Utilization of the pharmacy library

State pharmacy laws

Neatness and uniformity in preparing the prescription label

Hexachlorophene-containing detergents

The monthly ward drug inspection

Dispensing fatigue

Sterility tests on some hospital manufactured ophthalmic preparations

Formulations for the Dietary Service

The prescription balance test

The correct use of the ointment tubing equipment

Recurring reports

Use of the *American Hospital Formulary Service*

Chelates in soap solutions

Summary of articles in the current AMERICAN JOURNAL OF HOSPITAL PHARMACY.

Highlights of the Institute on Hospital Pharmacy

Ethics and the hospital pharmacist

Narcotic records—can they be simplified?

In summary, the weekly staff conference is a valuable communicative tool, as well as a refresher of professional skills. De-emphasization of parliamentary procedure and formality will produce a more effective pooling of ideas. The resulting decisions and enlightenment contribute to the wealth of professional service.

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stability of MORPHINE in aqueous solution

1. FORMULATION OF STABLE MORPHINE SOLUTION

by SHU-YUAN YEH *and* JOHN L. LACH

► ALTHOUGH ONE HUNDRED AND FIFTY YEARS have passed since morphine was first isolated from opium poppy, it is still one of the most potent of the analgesic drugs in medicine today. Morphine is unstable in aqueous solution as evidenced by discoloration. This discoloration of morphine solutions is believed to be due to an oxidation of morphine to the dimeric pseudomorphine. Of the many studies reported dealing with the stability of this analgesic in aqueous solution, the effects of hydrogen ion concentration[1,2,3,4] and atmospheric oxygen[5] appear to be the most important. Morphine in alkaline or neutral solutions deteriorates rapidly at room temperature whereas in acid solution it is relatively stable.[6] The presence of atmospheric oxygen in solutions containing morphine has also been reported to be responsible for this decomposition.[5]

A survey of the literature concerning the stability of aqueous morphine solutions indicates that certain precautions should be observed in the preparation of such solutions. These are as follows:

1. The use of neutral glass and addition of mineral acid to the solution to lower the *p*H. [5,7]
2. Addition of an antioxidant such as sodium bisulfite,[7,8,11] ascorbic acid,[10] sodium sulfite, or antipyrine.[9]
3. Replacement of air in the container with an inert gas.[3,11]
4. Use of bactericidal agents such as benzoic acid in place of high temperature sterilization.[12]
5. Storage of the preparations away from light.[5,13]

Experimental

Since the degradation of morphine is believed to involve the phenolic hydroxy group, it was felt that the stability of morphine solutions could be enhanced by the use of complexing agents or antioxidants which would block this route of oxidation. The purpose of this study was to qualitatively compare various agents with regard to their stabilizing effect. In this study morphine sulfate was employed in that the sulfate salt has been reported to be more stable than the hydrochloride.[10]

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Reagents

Morphine Sulfate U.S.P. recrystallized from alcoholic aqueous solution and dried under vacuum for six hours. m.p. 250°

Stabilizing agents: U.S.P. or analytical grade.

Deionized water.

Procedure

Accurately weighed quantities (0.15 Gm.) of morphine sulfate were placed in 100 ml. volumetric flasks containing 50 ml. of deionized water or buffer together with varying amounts of stabilizing agent under study. Volumetric flasks of 100 ml. size were used in order to insure the presence of a sufficient amount of atmospheric oxygen. The flasks were sealed with silicone covered stoppers and placed in an oven at 95°. No attempt was made here to follow the amount of decomposition of morphine quantitaively; only physical changes in the solutions were observed at various time intervals.

Discussion

Solutions containing morphine sulfate and various organic acids, Table I-A, showed some degree of increased stability over a solution of just morphine sulfate. This increase in stability may be due, in part, to complex formation resulting from the molecular interaction of the organic acid and morphine rather than a *p*H effect since a morphine sulfate solution containing benzoic acid in a citrate buffer *p*H 3 did not give an increase in stability over a solution of morphine sulfate and benzoic acid. It is interesting to note that a decrease in the stability was observed in such a system (Formulas A_1 and A_{14}).

A study employing the sodium salts of those organic acids was undertaken in view of the limited solubility of these acidic agents. The stability observed, in morphine sulfate solutions containing these sodium salts and listed in Table I-B, was decreased considerably over that of the organic acids, this decrease due chiefly to the alkalinity of the solutions.

Stability data obtained from a study of morphine solutions containing various complexing agents and listed in Table I-C, were also unsatisfactory in that discoloration was noted in one day. The observed color of these solutions was due to the decomposition of morphine and in part to some degradation of the complexing agents used; agents such as aminopyrine, acetanilid, antipyrine, and hydroquinone are in themselvess relatively unstable at the temperature employed in this study. It has been reported by Steinbrenck[9] that morphine is both solubilized and stabilized in 0.01 N hydrochloric acid solution containing sodium sulfite by the use of antipyrine. Our results indicate that the stability of morphine sulfate in the presence of sodium sulfite and antipyrine is probably due to the sodium sulfite and not the antipyrine.

Since the results obtained in the formulation studies conducted were unsatisfactory, a series of morphine sulfate solutions containing sodium bisulfite together with various agents, listed in Table II, was further investigated. Data obtained in this study indicated that the concentration of sodium bisulfite in solution was more important that the presence of a buffer and/or additional stabilizing agents with regard to the stability of these morphine solutions.

TABLE I. STABILITY OF MORPHINE SOLUTIONS WITH VARIOUS ORGANIC ACIDS, SALTS OF ORGANIC ACIDS AND COMPLEXING AGENTS.

A. CONTAINING ORGANIC ACIDS.

CODE NO.	STABILIZING AGENTS USED			DEVELOPMENT OF COLOR IN DAYS AT 95°
A	No Agent			1
A_1	Benzoic Acid	0.1	Gm.	4
A_2	Barbituric Acid	0.1	Gm.	1
A_3	Tartaric Acid	0.3	Gm.	4
A_4	Salicylic Acid	0.1	Gm.	5
A_5	p-Hydroxybenzoic Acid	0.1	Gm.	3
A_6	m-Hydroxybenzoic Acid	0.1	Gm.	4
A_7	p-Aminobenzoic Acid	0.1	Gm.	0.5
A_8	Lactic Acid 6 gtt.	0.1	Gm.	4
A_9	0.2 M Phosphate Buffer at *p*H 3.0			1
A_{10}	Citric Acid	0.1	Gm.	4
A_{11}	Glycocoll Mixture at *p*H 2.0			2
A_{12}	Glycocoll Mixture at *p*H 3.0			2
A_{13}	0.2 M Citrate Buffer at *p*H 4.0			1
A_{14}	Benzoic Acid 0.2 M Citrate Buffer at *p*H 3.0	0.1	Gm.	1
A_{15}	Ascorbic Acid	2.5	Gm.	immediately
A_{16}	Ethylenediaminetetra-acetic Acid	0.025	Gm.	6
A_{17}	Ethylenediaminetetra-acetic Acid	0.2	Gm.	7

B. CONTAINING SALT OF ORGANIC ACIDS.

Disodium, Calcium Ethylenediaminetetraacetic Acid
Disodium Ethylenediaminetetraacetic Acid
Sodium Salicylate
Sodium p-Hydroxybenzoate
Sodium p-Aminobenzoate
Sodium Formaldehyde Sulfoxylate
Sodium m-Hydroxybenzoate
Sodium Saccharin
Sodium Azide
n-Butyl p-Aminobenzoate
All of the above formulas developed color within one day.

C. CONTAINING COMPLEXING AGENTS.

Polyethylene Glycol 6000	Polyvinylpyrrolidone
Urea	N,N-Dimethylacetamid
Acetanilid	Aminopyrine
Ephedrine Sulfate	Nicotinamide
Antipyrine	Hydroquinone

Sorbitol (from 1.5% to 70%, 4 formulas)
All of the above formulas developed color within one day.

Therefore, an additional series of formulas containing various concentrations of sodium bisulfite were prepared and listed in Table III. These solutions were sealed in 2 ml. ampuls, placed in an oven at 95° and observed at periodic intervals for any color change. Formulas containing a concentration of 0.5 percent W/V of sodium bisulfite and 0.3 percent morphine sulfate were stable and showed no discoloration after 15 months' storage. It should be pointed out here that morphine solutions containing one percent sodium bisulfite together with benzoic acid; ethylenediaminetetraacetic acid; and 0.2 M citrate buffer, *p*H 3.0 (Formulas S_1,S_2,S_3) gave a stability of 40-60 days, considerably less than that for morphine solutions containing 0.5 percent or greater of sodium bisulfite. This decrease in stability is probably due to the acidity of these solutions, in that bisulfite ion is less stable in an acidic media. Sodium bisulfite in strong acidic solution exists principally as sulfurous acid whereas in alkaline solution it exists principally as sulfite ion. From the dissociation constants of sulfurous acid, $K_1 = 1.77 \times 10^{-2}$ $K_2 = 6.24 \times 10^{-8}$ it can be shown that bisulfite ion concentration is greatest at *p*H 4-5.

Since in the preparation of injectables it is desirable that the hydrogen ion concentration be close to neutrality, a formula was prepared containing one percent sodium bisulfite in 0.1 M phosphate buffer, *p*H 7.0.

TABLE III. FORMULAS CONTAINING SODIUM BISULFITE AND SEALED IN AMPULS.

CODE No.	STABILIZING AGENTS USED			DEVELOPMENT OF COLOR IN DAYS AT 95°
S_1	Benzoic Acid	0.1	Gm.	40
	Sodium Bisulfite	0.5	Gm.	
S_2	Ethylenediaminetetra-acetic Acid	0.05	Gm.	40
	Sodium Bisulfite	0.5	Gm.	
S_3	Sodium Bisulfite	0.5	Gm.	60
	0.2 M Citrate Buffer at *p*H 3.0			
S_4	Sodium Bisulfite	0.25	Gm.	No color changes after 15 months
S_5	Sodium Bisulfite	0.5	Gm.	"
S_6	Sodium Bisulfite	1.0	Gm.	"
S_7	Sodium Bisulfite	1.5	Gm.	"
S_8	Sodium Bisulfite	2.0	Gm.	"
S_9	Sodium Bisulfite	2.5	Gm.	"
S_{10}	Sodium Bisulfite	0.5	Gm.	"
	Sodium Chloride	0.3	Gm.	
	0.1 M Phosphate Buffer at *p*H 7.0			

TABLE II. FORMULAS CONTAINING SODIUM BISULFITE AND OTHER AGENTS.

CODE No.	STABILIZING AGENTS USED			DEVELOPMENT OF COLOR IN DAYS AT 95°
M_1	Ascorbic Acid	0.25	Gm.	immediately, due to
	Sodium Bisulfite	0.3	Gm.	ascorbic acid
M_2	Sodium Bisulfite	2.5	Gm.	60
	Antipyrine	0.5	Gm.	
M_3	Sodium Bisulfite	0.25	Gm.	60
	Antipyrine	0.25	Gm.	
M_4	Menadione Sodium Bisulfite	0.2	Gm.	30
	Sodium Bisulfite	0.1	Gm.	
M_5	Menadione Sodium Bisulfite	0.05	Gm.	2
	Sodium Bisulfite	0.025	Gm.	
M_6	Sodium Formaldehyde Sulfoxylate	0.1	Gm.	10
	Sodium Bisulfite	0.25	Gm.	
M_7	Benzoic Acid	0.1	Gm.	25
	Sodium Bisulfite	0.25	Gm.	
M_8	Ethylenediaminetetra-acetic Acid	0.025	Gm.	25
	Sodium Bisulfite	0.25	Gm.	
M_9	Sodium Bisulfite	0.25	Gm.	33
	0.2 M Citrate Buffer at *p*H 3.0			
M_{10}	Sodium Bisulfite	2.5	Gm.	Colorless after six months
	0.2 M Citrate Buffer at *p*H 3.0			

The stability of this preparation was found to be comparable to solutions containing morphine sulfate and sodium bisulfite.

Conclusion

Morphine sulfate solutions can be stabilized by the use of suitable antioxidants such as sodium bisulfite. In addition to its role as an antioxidant it has been found that sodium bisulfite undergoes addition formation with morphine. The results dealing with a study of this addition phenomenon are presented in Part II of this investigation.[14]

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DISPOSABLE TYPE VIALS

for adding medications to large volume parenterals

by Robert C. Bogash, Norman de la Chapelle, Rosemarie Sowinski *and* Diane Downes

► ONE GROWING PHENOMENON in modern hospital operation is that of the disposable product. This phenomenon has spawned a variety of products for patient care and hospital operations generally, ranging from enemas to sterile culture media. Time and experience proved some disposable products highly advantageous. Conversely, other products have been shown to be of no appreciable value compared to their nonexpendable counterparts.

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During the initial presentation to hospitals, as a consumer market, the disposable concept generally was viewed with skepticism. That reticence we feel can be attributed to two major factors; novelty and insufficient objective data to substantiate the claims made for the individual products. The claims made can be categorized generally as safety, economy, and convenience. While there is yet no unanimity of opinion re-

garding disposables it is apparent they have attained a status of well accepted adjuncts in current hospital procedures.

We believe that, however widely accepted a particular product might be, acceptance by the individual hospital contemplating its use must be premised on the conditions that exist in that hospital. Each disposable product should be carefully and objectively compared with the counterpart it is intended to replace. It, therefore, is conceivable that the same evaluation may differ when done in different geographic areas. The resultant difference might be slight or significant depending upon the conditions involved. The comparison should include consideration of additional factors: intangible costs, acceptability by staff, and patient relations. Together with direct costs there is made available a true reflection of the product's applicability in the individual hospital.

It was in order to satisfy the needs[1*] of individual applicability and suitability that this department several years ago reported our findings on loaded cartridge medications.[2*] Recently the Incert System was made available as a vehicle designed to introduce sterile medications into intravenous solutions, obviating the use of the traditional, and potentially hazardous, syringe-needle method. This Incert System[3*] in addition to being a disposable unit also introduces a change in the traditional technique of adding a medication to intravenous solutions. The Incert System consists of a spouted vial containing sterile medication and so constructed that when inverted and introduced into the large aperture of the rubber cap on the infusion bottle, the vacuum differential transfers the contents of the Incert vial into the intravenous solution. The small vial is then removed and discarded. Of additional interest was the pressure pump mechanism which permits solubilization of lyophilized powders and transferal into the intravenous solution while maintaining a closed system.

Because of the nature of this system and the technique involved in using it, it was felt that it should be evaluated by a triumvirate consisting of members of the Departments of Nursing, Methods Analysis and Pharmacy.

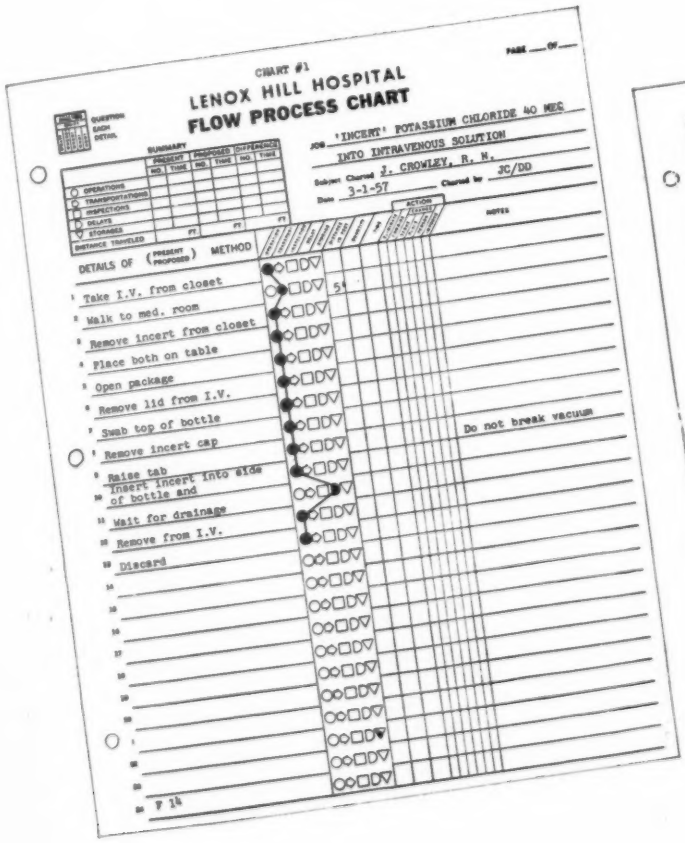
CHART #1

LENOX HILL HOSPITAL

FLOW PROCESS CHART

JOB 'INCERT' POTASSIUM CHLORIDE 40 MEQ INTO INTRAVENOUS SOLUTION

Subject Charted J. CROWLEY, R. N.

Date 3-1-57 Charted by JC/DD

DETAILS OF (PRESENT / PROPOSED) METHOD

1 Take I.V. from closet
2 Walk to med. room
3 Remove incert from closet
4 Place both on table
5 Open package
6 Remove lid from I.V.
7 Swab top of bottle
8 Remove incert cap
9 Raise tab
10 Insert incert into side of bottle and
11 Wait for drainage
12 Remove from I.V.
13 Discard
14
15
16
17
18
19
20
21
22
23
24
25
26 F 14

NOTES: Do not break vacuum


CHART #2

LENOX HILL HOSPITAL

FLOW PROCESS CHART

JOB AMPUL POTASSIUM CHLORIDE 40 MEQ INTO I.V. CONTAINER - 2 PIECE SYRINGE

Subject Charted J. CROWLEY, R. N.

Date 3-1-57 Charted by JC/DD

DETAILS OF (PRESENT / PROPOSED) METHOD

1 Take I.V. from closet
2 Walk to Med. Room
3 Take syringe from box
4 Open package
5 Take needle from box
6 Open package
7 Attach needle to syringe
8 Place unit in container
9 Take med. from drawer
10 Take sponge out of cont.
11 Crack ampul
12 Remove lid from bottle
13 Remove stopper
14 Draw up med. into syringe
15 Adjust solution
16 Wipe top of bottle
17 Inject med. into I.V.
18 Remove needle
19 Separate syringe
20 Flush with water
21 Carry to container
22 Deposit in container
23
24
25 F 14

NOTES: Possible cut finger; Possible contamination

Evaluation

A time-motion study was conducted to determine the efficacy and perhaps economy of adding to intravenous solutions medications by means of a standard two-piece glass syringe and a disposable type vial.

The standard two-piece glass syringe used in the time studies was the Multifit[A®] and the disposable vial was the Incert.[B®]

Number of Comparisons

Detailed studies were recorded on 100 admixtures via the glass syringe and 200 admixtures introduced by the disposable vial.

In both cases the medication was potassium chloride 40 milliequivalents.

Factors Considered in the Comparison

Direct costs were based on current salaries paid to nursing and ancillary personnel and current purchase records of syringes, needles and potassium chloride ampuls,

Registered Nurses, General Duty—$320.00/Month

Potassium Chloride Ampuls, 40 Milliequivalents (mEq.)—$0.17 ea.

Potassium Chloride Incerts, 40 mEq.—$0.321 ea.

Observations Regarding Efficiency

1. The use of disposable vials saved more than 1 minute of nurses' time per admixture. (See Chart 1.)

2. Using the two-piece glass syringe 22 actions were required compared to 13 for the disposable vial. (See Chart 2.)

3. Of the 22 steps necessitated with the two-piece glass syringe 12 are of an operational nature in handling the syringe compared to 5 operations in the 14 steps required in using the disposable vial.

4. The overall reduction in 'set up' and operational movements permits completion of an admixture in 60 percent less time and with 36 percent fewer movements. (See Chart 3.)

5. There are fewer opportunities for contamination.

6. The disposable vial system could present a problem if fractional doses are required. To date the products available are those which are usually added in their entirety to intravenous solutions.

7. At the present time there are six medications available in disposable vials. As additional medications are made available the economies, particularly those attributed to nursing time, are easier to consolidate and therefore more manageable with respect to use in other nursing efforts.

Observations Regarding Economy

1. The pure cost of potassium chloride 40 mEq. ampuls ranges from 17 cents to 37* cents per ampul as compared to that of potassium chloride Incerts at 32.16 cents, while it costs 3.14 cents more to handle and use the ampuls. (See Chart 3.)

2. Use of disposable vials obviates the 18 cent cost expended in Central Sterile Supply in the collection, handling, cleaning, sterilization, packaging, and delivery of needles and syringes.

3. Nurses' time saved, (62 seconds) per admixture is 3.14 cents. (See Chart 3.) (How this particular economy is most constructively utilized is a problem of both nursing and hospital administration.)

[A] Becton Dickinson

[B] Baxter Laboratories

*Dependent upon source of supply

Chart 3. Flow Chart Times

Standard 2 Piece Glass Syringe			
	Time Spent		
Operation	Min.	Max.	Av.
I. Get I.V.-Select and prepare syringe	19″	24″	22″
II. Get med. Prepare and crack ampul	10″	23″	16″
III. Prepare I.V. for injection	12″	26″	19″
IV. Draw up med. and adjust solution	12″	35″	24″
V. Swab I.V. and inject med. into I.V. Remove needle	6″	21″	13″
VI. Disassemble syringe, flush with water, place into container	9″	12″	10″
Average Total Time & Cost			104″
			$.053

Disposable Vial			
	Time Spent		
Operation	Min.	Max.	Av.
I. Get I.V. and Incert, place on table	12″	16″	14″
II. Break Seal on I.V., open Incert, remove cap	6″	18″	14″
III. Swab Incert, wait for drainage	11″	14″	12″
IV. Remove from I.V., discard	1½″	3″	2″
			42″
			$.0216

Chart 4. Summary of Cost Factors

Standard 2 Piece Glass Syringe	Time	Cost	Disposable Vial	Time	Cost
1. Average time factor in administering potassium chloride 40 mEq.	104″	$0.0534	1. Average time factor in administering potassium chloride Incert 40 mEq.	42″	$0.0216
2. Cost of handling syringe and needle		0.18			0.3216
3. Cost of ampul potassium chloride 40 mEq.		0.27*			
Total		$ .503	Total		$0.3432

*This factor can vary from $0.17 to $0.37 dependent upon source of supply—a median average is therefore recorded.

4. Combining the economies of direct cost, nursing time and central sterile supply, shows a 16.08 cent saving per admixture. Purchase records show 1,800 ampuls purchased of potassium chloride, 40 mEq., in 1958. The extension of this figure (1800) with the 16.02 cents saving, produces a theoretic annual saving of $289.44 for potassium chloride admixtures alone.

5. The overhead, storage, and maintenance of disposable vials is comparable to ampuls.

Observations Regarding Safety

1. The Incert System of disposable vials reduces to a minimum possible air-borne contamination since the medication is transferred from one sterile container to another without exposure to air.

2. It is felt that the disposable vial system minimizes the potential transmission of infectious hepatitis.

3. There is greater accuracy in delivering a premeasured quantity of medication.

4. Nursing personnel commented that they like to use the disposable vial since it represents a closed system and fewer possibilities for cut fingers experienced in opening and handling ampuls.

5. The disposable vial system could present a problem if fractional doses are required. To date the products available are those which are usually added in their entirety to intravenous solutions.

This comparative study has shown quite conclusively that disposable vial system is far more efficient, safe, and economical than the two-piece glass syringe for adding sterile medications to intravenous solutions.

While the results of this study reflect only direct costs, other considerations should also be taken into account. (See Chart 5.) From an overall economic aspect the disposable vial system becomes even more acceptable when one considers the economies realized in other departments such as Nursing, Central Sterile Supply, Storeroom, and Purchasing.

Chart 5. Hidden Costs—Not Recorded But Should Be Considered

Intangible Costs
Amortization cleaning equipment
Loss of nursing time — cut fingers
Moral cost of cases of infectious hepatitis
Reduction of syringe breakage
Reduced labor in Central Supply-Storeroom and Purchasing Departments

Acknowledgements

Our sincere appreciation is extended to Miss J. Crowley and other members of the Nursing Service without whose cooperation this study could not have been done, to Wyeth Laboratories for their continued interest in and support of our Methods Analysis Department, and to Baxter Laboratories for Incert products.

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USE OF VOLUNTEER SERVICE IN THE HOSPITAL

by ROBERT E. LAWSON

► FOR SEVERAL YEARS NOW we have been reading and hearing of the way the hospitals have been utilizing nonprofessional personnel in the operation of their pharmacies. The use of volunteer services should be considered a branch of the nonprofessional personnel segment. It can be stated, then, that if you are now using nonprofessional personnel in your pharmacy in any capacity you could safely make use of volunteer services.

The Pharmacy Department in University Hospital (Maryland) has utilized services of volunteers under the Woman's Auxiliary Board and Red Cross workers for a period of 14 months. During this time much valuable aid has been contributed to the department. Utilization of these volunteers has enabled us to accomplish many tasks which had previously been sidelined because of lack of time.

Justification

I feel no need to justify this presentation, for it is certainly not the intent of this paper to explain how volunteers can be utilized to take the place of a pharmacist. Rather, we wish to show how the volunteer can relieve the pharmacist of many of his routine, nonprofessional functions. If there is no one else to do this work the pharmacist must do it. The result is a waste of time and professional ability. There is a correspondingly lesser amount of time for providing pharmacy service. Proper utilization of volunteer workers can feasibly be a factor in counteracting the rising cost of hospital care. At this point, however, I wish to place special emphasis on a very important factor. It is especially important to consider volunteer services not as a means of free labor but instead as an augmentation to your staff to allow a better or additional service to be contributed to the patients' welfare. If you have recently tried to add a pharmacist to your staff I am sure that you will agree that their availability is critical. It may be that after proper study of work loads you will discover that some clerical work, prepackaging of drugs, and other menial tasks which have been performed by a pharmacist can be efficiently and effectively performed by use of volunteer personnel.

Selection

In University Hospital all volunteer workers are initially interviewed by a full-time, paid Director of Volunteer Services. The interview is followed by a guided tour of the various departments in the Hospital which have requested volunteers. It is during this tour that the Director of Volunteer Services has the opportunity to show the volunteer not only the good things about the Hospital but also how to cope witth some of the things she will find that are not so good or which are, perhaps, unpleasant. This is the time to teach the volunteers loyalty, discretion and ethics. The principal aim of the tour is to discover the volunteers' interest, experience, skills, and job preferences. Personal motivation, however, of the volunteer is not really an important factor as long as she is willing to work with limitations set by the hospital.[1]

Volunteers are not necessarily limited to ladies either. There is an increasing number of retired businessmen who are volunteering for work in hospitals. There is no maximum age limitation. Starting this year University Hospital has accepted girls and some boys aged 14 or older. The name of "Volun-teens" has been

Presented at the Annual Convention of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Cincinnati, Ohio, August, 1959.

ROBERT E. LAWSON is Director, Pharmaceutical Services, University Hospital, University of Maryland, Baltimore 1, Maryland.

assigned this younger group and they have contributed much to the program during the summer months.

Policies and Attitudes

The volunteer worker is treated like a regular, paid employee. An attitude of tolerance because of the volunteer's lack of pay has not been allowed to prevail. This, of course, ultimately resulted in a loss of a few volunteers, but in general this strengthens the program rather than weakens it. The volunteers have regular designated hours (selected by them, but approved by the Director of Volunteers) and must sign in and must sign out. If the volunteer is unable to work at a scheduled time she must notify the Director of Volunteers in advance. The Director then, in turn, notifies the department concerned. The volunteer is assigned to a department of her choosing and remains with that department until relieved by the Director of Volunteers. She is given a 30-minute lunch period which is taken at the convenience of the department. She must pay for her own lunch. This sounds like rather harsh treatment of one who has volunteered her services but the philosophy behind this attitude is sound. The volunteer feels that she is doing a worthwhile job and that the Hospital is depending on her services. This develops a firm loyalty to the department and the hospital and results in a good public relations program. Those who remain in the program are there to work and there is no foolishness or attitude of social gathering on the part of the volunteer.

Awards for service time are made in the form of a military type of service stripe designating the years of service which have been volunteered. Outstanding service or individual deeds are recognized by the presentation of a token gift such as a book or flowers. Before any volunteer is placed in a department, the Director of Volunteer Services comes into that department to make a physical survey of the work area of the volunteer, the job or jobs she will be asked to perform and the supervision she will expect to receive. In collaboration with the department head, a detailed job description is developed. If the job is to prepackage tablets, this job description covers each step from selection of empty bottles to the file control number inspection. The job description is kept on permanent file in the Volunteer Service Office and the department concerned. One copy is given to each volunteer worker as a guide.

Utilization

All the basic principles of supervision of nonprofessional personnel are applied to supervision of volunteer workers. The volunteers have worked in our Pharmacy Department primarily in our prepackaging program. This is always under the supervision of a registered pharmacist and the volunteers have been responsible for approximately 75 percent of our total prepackaging in both inpatient and outpatient services. In addition, the volunteer has washed bottles and equipment, performed various clerical tasks such as typing, filing, pricing of drug charges and mimeographing forms used by the Pharmacy.

Every effort is made to assure that the volunteer is properly placed in a department where she will do her best job. A volunteer should not be "talked into" a department which has a shortage of personnel by stressing good points of that department and underemphasizing its bad points. It has been determined that a department is better off without any volunteers than with one who is not interested in her work. The job then is to develop a corps of satisfied useful volunteers. Volunteers do not stay if they are not satisfied. The hospital does not want them if they are not useful.[2]

The mechanism for transferring a volunteer should be kept as simple as possible. In our Hospital, if the volunteer is not working out satisfactorily, the department head notifies the Director of Volunteers who, in turn, tries to find a job more suitable for the volunteer. If the volunteer wishes a transfer she also notifies the Director of Volunteers who attempts to place her in another service, and to replace her with another worker. There are usually no hurt feelings in such transfers because if the volunteer is not satisfied the department usually is glad to have her leave also. The reverse of this situation also holds true.

Conclusion

The use of volunteer workers has proved eminently satisfactory for the Department of Pharmaceutical Services in University Hospital. This program has given us many valuable hours which we have needed to institute new procedures and to change old procedures. We have found that the intelligence and motivation of these people are above the average. We get a good number of doctors' wives, those of retired military officers and of outstanding and notable public officials. In many instances both my pharmacy staff and I have been able to talk with these people and to clear up many previous misunderstandings and prejudices which exist concerning the local drug stores, third party industrial medical insurance and, of course, our own Hospital. I believe that this close contact with the citizens has contributed greatly to our hospital public relations program and that we, as pharmacists, have a better understanding concerning the public's attitude toward pharmacy and hospitals.

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A A A S

American Association for the Advancement of Science

PHARMACY SECTION MEETING

Chicago, December 26 - 29, 1959

by JOHN CHRISTIAN

► THE PHARMACY SECTION of the American Association for the Advancement of Science held eight sessions December 26 through December 29 in Chicago, Illinois. A total of forty-eight contributed papers on various studies was reported and one symposium was held. Over three hundred persons registered as having attended one or more of the pharmacy section meetings.

The AAAS Council, the governing body of the Association, elected Dr. Joseph Swintosky, Research Division of Smith, Kline and French Laboratories, Philadelphia, Pennsylvania, as a Vice-President of the Association and elected Dr. Don E. Francke, University Hospital, University of Michigan, to serve on the Committee-at-Large of the Section for a four-year term. Dr. Swintosky will serve as Chairman of the Section for the coming year and will preside at the Philadelphia meeting in December, 1960.

JOHN CHRISTIAN, PH.D., is Professor of Pharmacy at Purdue University School of Pharmacy, Lafayette, Indiana, and is Secretary of the Pharmacy Section of the American Association for the Advancement of Science.

Vice-President's Address Is Highlight

Of major interest to the group in attendance was the stimulating vice-presidential address on "Professionalism and the Pharmaceutical Scientist," presented by Dean Glenn L. Jenkins. A symposium entitled "The Scientist's Part in Protection of the Public, Part I: Food, Drug, Cosmetic and Hazardous Chemical Problems and Part II: Food Additive Legislation," also attracted considerable interest, not only on the part of the pharmaceutical scientists in attendance, but also by many individuals from other scientific disciplines. Dr. Joseph Swintosky and Dean Glenn L. Jenkins gave introductory remarks and served as presiding officers over the sessions. Dr. Bernard E. Conley, Secretary of the Committee on Toxicology of the American Medical Association gave a discussion of the labeling of hazardous chemicals. Dr. William F. Bousquet, Assistant Professor of Bionucleonics at

Purdue University, presented the problems of pharmaceutical ingredients legislation and approaches to solving them. Dr. Bousquet emphasized the importance of radioisotope techniques in studying food and drug residues and formed metabolites. The role of the cosmetic scientist in protecting the public health was covered by Raymond E. Reed, Vice-President of the Toni Company. Dr. John H. Rust, Head of the Section on Nuclear Medicine at the University of Chicago, spoke on the applications of radioactive isotope tracer techniques to studying the food additive problem. He emphasized the need for education in isotope tracer techniques to supply trained personnel for food research now necessary under present food additive legislation. Problems in evaluating the safety of international food additives and unintentional food additives were set forth by Dr. O. Garth Fitzhugh, Chief of the Toxicity Branch of the Food and Drug Administration and Dr. Arnold J. Lehman, Director of the Division of Pharmacology of the Food and Drug Administration, respectively. Dr. Edward J. Matson, Director of Scientific Administration for Abbott Laboratories, explored the philosophical question of scientific judgment in law and regulation. He emphasized the need for sound scientific judgment based on known facts in arriving at conclusions regarding levels of toxic and carcinogenic substances in foods for human consumption. The role of the scientific expert under recent food laws was summarized by Bernard L. Oser, President of Food and Drug Research Laboratories, Inc. The symposium was terminated with an hour-long question and answer session on current food, drug, and cosmetic problems.

Hospital Pharmacy Papers

In addition to the above-mentioned program, the hospital pharmacy group had a most informative and well-attended full-day session under the guidance of Dr. George F. Archambault and Mr. Joseph A. Oddis. The meeting was held in the recently-completed facilities of the American Hospital Association. The following organizations were represented: American Society of Hospital Pharmacists, American Pharmaceutical Association, Illinois Society of Hospital Pharmacists, American Hospital Association, National Association of Boards of Pharmacy, U. S. Public Health Service, Illinois Hospital Association, and the National Institutes of Health. Luncheon, entertainment and dinner were sponsored by E. R. Squibb & Sons, Mead Johnson and Company, and McKesson and Robbins, Inc., respectively.

Subjects of papers presented at the hospital pharmacy session varied from one on "Some Social Forces That Will Affect the Hospital and the Hospital Pharmacy," by Mr. Ray E. Brown, Administrator of the University of Chicago Clinics, to "The Solubilization of Iodine with Tween 20" by Edward Deeb, Pharmacist at the Veterans Administration Hospital in Pittsburgh. A complete listing of the papers presented appeared on page 608 of the November (1959) issue of the Journal.

Contributed Papers

Professor George L. Webster, Dean, College of Pharmacy, University of Illinois, opened the contributed paper sessions which consisted of the presentation of the results of original investigations. Egil Ramstad and co-workers at Purdue University presented a series of six papers describing work done on plant biogensis and metabolism using radioactive tracer techniques. C. T. Peng, University of California, discussed quenching of fluorescence in liquid scintillation counting and in a second paper the fate of tumor implants in rats. The distribution of C-14 meprobamate in rat brain was discussed by J. L. Emmerson, T. S. Miya, and G. K. W. Yim of the Pharmacology Department, Purdue University. Herbert Schriftman, Wyeth Laboratories, spoke of the applications of paper chromatography and electrophoresis to the assay of pharmaceutical products. An improved 4 pi, whole body liquid scintillation counter was described by B. G. Dunavant and J. E. Christian of the Bionucleonics Department at Purdue University; and J. P. Vacik and J. E. Christian from the same department described the application of neutron activation analysis to the micro analysis of gold containing pharmaceuticals. G. Levy, University of Buffalo, described the physical-chemical basis of the buffered aspirin controversy; D. E. Guttman, Ohio State University, discussed the solubilization of riboflavin; J. Autian, University of Michigan, discussed the binding of drugs by plastics; and M. L. Eichmann, Ohio State University, presented information concerning the interactions of xanthine molecules with serum albumin.

Other papers presented were: Methods of Synthesis of Tetrahydroquinolizonium Salts, Color-Coding of Drug Dosage Forms, Hydration of Procaine Base, Evaluation of Suppository Bases, The Social Psychology of Prescription Writing, Effects of Physostigmine on Chick Eggs, Pharmacological Prevention of Acute Heart Failure, and Spray-drying of Tablet Granulations. These papers were delivered by D. M. Stuart, Oregon State College; R. G. Brown, University of Texas; W. A. Strickland, Jr., University of Arkansas; J. Anschel, Warner-Lambert Research Institute; E. J. W. Hall, University of Texas; V. A. Green, University of Texas; J. W. Ingalls, Jr., Long Island University; A. M. Raff, Smith, Kline and French Laboratories, respectively.

This meeting proved to be one of the most successful meetings of the Pharmacy Section of the AAAS in recent years and was exceedingly well attended.

American Society of Hospital Pharmacists affiliated with American Pharmaceutical Association

Dear Hospital Pharmacist:

Yours is a vigorous growing specialty in a proud and honored profession. Wouldn't you like to join with the more than 3,100 of your fellow hospital pharmacists who are sharing ideas, their time and talents, to improve and maintain high standards of service to hospital patients through the American Society of Hospital Pharmacists? And wouldn't you like to be among those of your associates in other professions on your hospital staff who contribute to the advancement of their respective professions by taking part in the activities of their professional organizations?

Hospital pharmacy has come a long way in a relatively few years. Its progress strikingly parallels the growth of the American Society of Hospital Pharmacists. We have all profited, professionally and financially, from the activities of the ASHP, and the collective and individual efforts of its members.

Just as in any major professional specialty, our members will want to belong to and be a part of the parent Association, in your case and mine, the American Pharmaceutical Association. Its proud heritage of more than a hundred years of service and progress can be yours along with your membership in the American Society of Hospital Pharmacists.

The cost is nominal. The satisfaction is great. Please consider this a personal invitation to become a member today. May we hear from you soon?

Sincerely,

Vernon Trygstad

VERNON O. TRYGSTAD
President

Veterans Administration
Vermont Avenue, N. W.
Washington 25, D. C.

your responsibility in membership activities

► THE SOCIETY'S COMMITTEE ON MEMBERSHIP AND ORGANIZATION in cooperation with the Division of Hospital Pharmacy at the Headquarters of the American Pharmaceutical Association in Washington has organized a plan for membership promotion. Members of the Committee on Membership and Organization serve as National Area Chairman. In addition, local area chairman have been appointed in each state and affiliated chapter. Contacts are made and coordinated through the Division Office with a series of letters to the Area Chairman and prospective members.

In recognition of the work being carried out by Louis Jeffrey and his Committee and Paul Parker in the Division of Hospital Pharmacy, the names of individuals serving as Area and Local Chairman are listed.

COMMITTEE ON MEMBERSHIP AND ORGANIZATION

From the Chairman:

Are you doing your share? Are you carrying out your responsibilities and obligations?

Many times we are asked these questions. It doesn't really confine itself to organizational work or to charitable causes, but it is a philosophy which should be a part of our everyday lives, especially in our profession. The work of the Committee on Membership and Organization has, in the opinion of its current Chairman, always been one of the SOCIETY'S most vital activities. During the forthcoming year 65 members of this Committee will contact approximately 1,500 prospects, to encourage them to become members of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS and the American Pharmaceutical Association. The responsibility of obtaining new members should not be confined solely to this Committee. With more than 3,000 members to assist in this important phase of SOCIETY activity, the work of these 65 members will be lightened and appreciated.

I think that it would be well for every hospital pharmacist to give attention to President Trygstad's letter appearing on the previous page.

Would you all share this responsibility with this Committee?

LOUIS JEFFREY, *Chairman*

► National Area Chairman:

Herbert R. Riemen
238 Orchard Place
Lackwanna, New York

	Local Area Chairman
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NORTH CAROLINA	Margaret Gretz
PUERTO RICO	Lee Neidlinger

Therapeutic Trends

edited by WILLIAM JOHNSON

U-5641

U-5641 is a phenothiazine derivative which has been studied for its diuretic effect. U-5641 differs structurally from chlorpromazine in having an oxygen attached to the sulfur in the phenothiazine ring and in having a 2-(1-pyrrolidinyl)ethyl side chain instead of a 3-dimethylaminopropyl group. This drug was reported to be an effective diuretic in experimental animals, and this study was undertaken to determine its effectiveness in human beings. The observations by Pontidas and Mills are reported in *Antibiot. Med. Clin. Therap.* 6:715 (Dec.) 1959. Fourteen patients with arteriosclerotic heart disease (with the exception of two patients) were studied. In the results presented, no significant change in urine volume, urinary sodium, or body weight after either 500 or 1,000 mg. of U-5641 was noted. In contrast, mercaptomerin gave a significant increase in urine volume and sodium excretion and a significant decline in body weight. These observations are in contrast to those of an earlier study in which significant diuretic effect and a comparative potency close to that of chlorothiazide was reported. The explanation of this discrepancy is not clear; however, it is possible that differing experimental conditions may have been responsible. The U-5641 for this study was supplied by the Upjohn Company.

WILLIAM E. JOHNSON

Ficus Protease in Various Types of Leg Ulcers

Evaluation of this new enzymatic debriding agent is presented in *Antibiot. Med. Clin. Therap.* 6:707 (Dec.) 1959 by McCormick and Olansky. This study reports on effective concentration and length of therapy. Concentrations of 7.7 percent and 1 percent were used. The 1 percent concentration appears to give the maximum debriding action without significant side effects, while the 7.7 percent concentration caused irritations of the surrounding, partially damaged tissues, resulting from incomplete discrimination between viable and partially viable tissues by the enzyme. The average length of therapy was from two to three days when dressings were changed twice daily. Although debridement was obtained to a satisfactory degree, it must be remembered that this is adjunct therapy and is only a preparation for definitive treatment. Ficus protease is a lyophilized protease extracted from the latex of a variety of fig tree. It was supplied for this study as Debricin by the Johnson and Johnson Department of Clinical Research.

DALE R. HYDER

Controlled Study of G27 202 in Rheumatoid Arthritis

Experiment showed G27 202 (p-hydroxyphenylbutazone) to be an anti-inflamatory agent equal in potency to phenylbutazone but producing few of the side effects associated with that drug. This study by Cardoe was conducted as a double blind trial using G 27 and a bland tablet. The purpose of this trial was to test the effect of the drug in rheumatoid arthritis. Thirty patients were used in the trial. Fifteen were given 200 mg. G27 twice daily with or after food and the others were given bland tablets of the same size, shape and color. The chief results were loss or reduction of morning stiffness in many of the patients using G27. Patients who were taking G27 also showed an increase in the strength of grip and loss or decrease of pain. There was a slight increase in weight in the patients taking G27 which may suggest fluid retention; however, there was no swelling of the feet recorded. The results, which were reported in *Annals Rheumatic Dis. 18*:244 (Sept.) 1959, seemed to indicate that G27 202 has analgesic and anti-inflammatory properties equal to those of phenylbutazone but not associated with any of the side effects seen with the latter drug. It is felt that although the drug appears to have no anti-rheumatic potency, it still should be considered an alternative therapeutic agent in the treatment of rheumatoid arthritis. The drug was supplied by Geigy Ltd.

RICHARD H. HARRISON

Kanamycin-Sulfisoxazole in Pulmonary Tuberculosis

Weiss *et al* report in *Antibiot. Med. Clin. Therap.* 6:731 (Dec.) 1959, on the use of sulfisoxazole in conjunction with kanamycin to prolong the time of therapy before the tubercle bacilli become resistant to the kanamycin. This proved to be valuable conjunctive

therapy. The authors suggest it may be worthwhile to investigate the ability of sulfisoxazole to delay the emergence of resistance to other antituberculous agents. Kanamycin was supplied by Bristol Laboratories, Inc.

DALE R. HYDER

Levomepromazine (Nozinan)—A New Neuroleptic Agent

This study was made with senile patients having various mental and nervous disorders. The group of ninety-eight persons was made up of 51 women and 47 men. About eighty percent of the group were over 70 years of age. The patients were divided for the study according to the presenting symptom (e.g. depression) or the clinic entity (e.g. schizophrenia). Evaluation of the effect was based on the change in the chief symptom or symptom complex. The dosages for senile patients must be carefully adjusted. With a few exceptions, all the patients in the study were maintained on 50 mg. daily or less. The average dose was 25 mg. daily. Hout and Kristof carried out this study and reported their results in *Canad. Med. Assoc. J. 81*:546 (Oct.) 1959. Nine patients developed intolerance to the drug and had to be discontinued. The major intolerance was severe drowsiness. The results of the study showed that the drug may be used successfully for senile patients with various nervous disorders. The drug was supplied by Poulenc Limited.

RICHARD H. HARRISON

Phenindione Sensitivity

Two cases of sensitivity of phenindione are discussed by Bingle and Shine in *The Lancet (London) 11*:377 (Sept. 19) 1959. The onset of the reaction is a little later than usual in drug allergies and since sensitivity reaction may be severe, immediate withdrawal of the drug is indicated at the first sign. The clinical and pathological findings of the reaction are described and treatment of such patients with other dicoumarin derivatives may be possible. A scheme of management is suggested.

DALE R. HYDER

Trimethidinium Methosulfate—Ganglionic Blocking Agent

Trimethidinum methosulfate is an asymmetric bisquaternary amine which blocks the ganglia of the autonomic nervous system and is reported to have additional antihypertensive effect by virtue of a more central action in the nervous system. Gifford reports in *Proc. Staff Meetings Mayo Clinic 34*:481 (Sept. 30) 1959, the use of this agent in a series of 13 patients. Trimethidinium methosulfate appears to be an effective antihypertensive drug that belongs to the family of ganglion-blocking agents. There were no clinical observations to indicate that it has any other action although from careful experiments with animals it had been postulated that it also acts more centrally in the nervous system. Thirteen patients were treated with this drug for periods of from six to seventeen months. It failed to reduce blood pressure in three patients, but dosage was not pushed to the limit of tolerance in any of these three. Side effects from ganglion blockade were observed in all but three cases. Trimethidinium methosulfate was supplied for this study as Ostensin by Wyeth Laboratories.

WILLIAM E. JOHNSON

Streptokinase and Streptodornase in the Treatment of Postoperative Vaginal Discharge

Streptokinase-streptodornase was used as the only local instillation in the cases of 100 women who had had vaginal hysterectomy and repair of a cyctocele. The indication for its use was the post-operative presence of a profuse, foul-smelling vaginal discharge noticed by the patient herself or by attendants. Re-Mine and Murphy report the use of this treatment in *Proc. Staff Meetings Mayo Clinic 34*:459 (Sept. 16) 1959. The medicament was prepared by mixing one vial of Varidase with 20 ml. of water and adjusting to proper viscosity (thin jelly) with lubricant jelly. The medicament was instilled into the vagina by catheter attached to syringe and the patient was required to remain flat in bed for one-half hour after instillation. Three instillations were the most required to completely eliminate the odoriferous discharge. In the 100 cases treated in this manner, the discharge was completely eliminated in 87 cases; in 8 cases it was greatly reduced: and in only 5 cases was there no appreciable relief. There was no instance of bleeding or other complications.

DALE R. HYDER

Metabolic Effects of Mytatrienediol in Man

A marked decrease of urinary calcium excretion and improvement in calcium balance followed a dose of 50 mg. of either mytatrienediol, or its analog 56-8246, given intramuscularly or orally. These weakly estrogenic compounds were studied for their metabolic effects. Calcium balance improvement was due to decreased calciuria and not to improved intestional absorption of calcium. The advantages of an agent in which metabolic and estrogenic potencies are separate points out the possibility that therapeutic benefits may be obtained without causing undesirable side effects such as feminization, gastrointestinal irritation or acceleration of tumor growth. This study by Spencer, Kabakow, Samachson and Laszlo was reported in *Clin. Endocrinol. and Metabolism 19*:1581.

KENNETH W. HUCKENDUBLER

Timely Drugs

Hycomine

COMPOSITION: Dihydrocodeinone (Hycodan) bitartrate, homatropine methylbromide, pyrilamine maleate, phenylephrine hydrochloride, ammonium chloride, and sodium citrate.
INDICATIONS: Antitussive, expectorant and decongestant.
DOSAGE: Adults, one teaspoonful; children, proportionately smaller.
PREPARATIONS: Syrup containing dihydrocodeinone bitartrate 5 mg., homatropine methylbromide 1.5 mg., pyrilamine maleate 12.5 mg., phenylephrine hydrochloride 10 mg., ammonium chloride 60 mg., and sodium citrate 85 mg., in each 5 ml.
PACKAGING: Bottles of 1 pint and 1 gallon.
SUPPLIER: Endo Laboratories.

Murel

GENERIC AND CHEMICAL NAMES: Valethamate bromide; phenylmethylvaleric acid-b-diethylaminoethyl-ester-bromomethylate
INDICATIONS: Antispasmodic, combining anticholinergic, musculotropic and ganglion-blocking action; indicated in spasm of gastrointestinal tract, genitourinary tract, biliary tract, and in active, latent or incipient peptic ulcer.
SIDE EFFECTS AND CONTRAINDICATIONS: Should be used with caution in patients with prostatic hypertrophy, glaucoma, and in presence of cardiac arrhythmias.
DOSAGE: Average dosage, 40 to 80 mg. daily.
PREPARATIONS: Tablets, sustained action, 10 mg. and 40 mg.; tablets, sustained action with 15 mg. or 30 mg. sodium phenobarbital; injection, 10 mg. valethamate bromide per ml.
PACKAGING: Bottles of 100 and 1,000 tablets; vials of 5 ml. injectable.
SUPPLIER: Ayerst Laboratories.

Naturetin

GENERIC AND CHEMICAL NAMES: Benzydroflumethiazide; 3-benzyl -3,4- dihydro-6- (trifluoromethyl) -1,2,4-benzothiadiazine-7-sulfonamide, 1,1-dioxide.
INDICATIONS: In control of edema and whenever diuresis is required for the treatment of any edematous state whether caused by cardiovascular and/or renal disease; specifically, in congestive heart failure, edema of premenstrual syndrome, edema and toxemia of pregnancy, nephrosis, etc.
SIDE EFFECTS AND CONTRAINDICATIONS: Gastrointestinal cramps in some patients, occasional reports of leg or abdominal cramps, pruritus, paresthesias, or rash; contraindicated in complete renal shutdown; dosage must be carefully regulated when added to regimen that includes a ganglionic blocking agent; should be used with cautions in patients with severely damaged kidneys.
DOSAGE: Edema, 5 mg. once daily initially, 2.5 to 5 mg. daily for maintenance; hypertension, 5 to 20 mg. daily, 2.5 to 15 mg. daily for maintenance.
PREPARATIONS: Tablets of 2.5 mg. and 5 mg., scored.
PACKAGING: Bottles of 100 and 1,000 tablets.
SUPPLIER: Squibb.

Orenzyme

COMPOSITION: Trypsin, chymotrypsin, and ribonuclease.
INDICATIONS: Oral therapy in contusions, crush injuries, fractures, sprains, dislocations; for systemic anti-inflammatory enzyme therapy.
SIDE EFFECTS AND CONTRAINDICATIONS: Should be used with caution in patients with abnormalities of blood clotting mechanism such as hemophilia, or with severe hepatic or renal disease.
DOSAGE: Initially, 2 tablets four times daily; as maintenance therapy or as adjunct to parenteral and/or buccal trypsin, 1 tablet three or four times daily.
PREPARATIONS: Tablets containing trypsin 68%, chymotrypsin 30%, ribonuclease 2%, equivalent to proteolytic activity of 20 mg. crystalline trypsin; enteric coated.
PACKAGING: Bottles of 48 tablets.
SUPPLIER: The National Drug Co.

Ornade

COMPOSITION: Chlorpheniramine (Teldrin) maleate, phenylpropanolamine hydrochloride, and isopropamide.
INDICATIONS: For relief of upper respiratory distress, combining a drying agent, a decongestant and an antihistamine.
SIDE EFFECTS AND CONTRAINDICATIONS: Should be used with cautions in presence of severe hypertension; should not be used in patients with glaucoma or prostatic hypertrophy.
DOSAGE: One capsule every 12 hours.
PREPARATIONS: Sustained relief capsules (Spansules) containing chlorpheniramine maleate 8 mg., phenylpropanolamine hydrochloride 50 mg., and isopropamide 2.5 mg.
PACKAGING: Bottles of 30 capsules.
SUPPLIER: Smith, Kline & French Laboratories.

Prinadol

GENERIC AND CHEMICAL NAMES: Phenazocine; 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2, 6-methano-3-benzazocine.
INDICATIONS: Narcotic and analgesic in general pain states, as preoperative medication, as anesthetic adjunct, and for postoperative restlessness and pain.
SIDE EFFECTS AND CONTRAINDICATIONS: Occasionally, nausea and vomiting, constipation, respiratory depression, hypotension, bradycardia, and tachycardia; contraindicated in cases of severe hepatic insufficiency, severe central nervous system depression or coma, in increased intracranial pressure, myxedema, and acute alcoholism, delirium tremens and convulsive disorders.
DOSAGE: For pain, 1 to 3 mg. intramuscularly every 4 to 6 hours; as preoperative medication, 1 to 2 mg. intramuscularly 45 to 60 minutes preoperatively; as anesthetic adjunct, 0.5 to 1 mg. intravenously.
PREPARATIONS: Injection containing 2 mg. per ml.
PACKAGING: Ampuls of 1 ml. in boxes of 10 and 100 ampuls, and multiple dose vials of 10 ml. in boxes of 1 and 20.
SUPPLIER: Smith, Kline & French Laboratories.

As the vice-president sees it—

JACK S. HEARD, *University of California Medical Center, Los Angeles*

► THIS MONTH I WOULD LIKE TO CALL YOUR attention to an up-and-coming group of hospital technicians—the Inhalation Therapists. This is a rapidly expanding field, and its practitioners have areas of common interest with hospital pharmacists. The inhalation therapist on the order of the physician administers a number of pharmaceutical preparations: wetting agents such as Alevaire and Turgemist, antibiotics, propylene glycol, and bronchodilators as well as oxygen and other gases.

There are about 1,000 members in the twenty-two chapters of the American Association of Inhalation Therapists. The Association is sponsored by the American Society of Anesthesiologists and the American College of Chest Physicians. While most of the members practice in hospitals, there are also sections for persons in service organizations (equipment rental companies, etc.). The majority of the therapists received their training on-the-job. A one year training course has been given at the University of Pennsylvania since 1956 and courses are being prepared at a number of other institutions, including the University of California at Los Angeles.

In efforts to improve their standards, the inhalation therapists are working closely with the anesthesiologists and chest physicians. These physicians assist in the training of the technicians and utilize their services in maintaining patients on inhalation therapy.

The inhalation therapist frequently plays a life-saving role in the hospital. He responds to emergency calls with oxygen equipment and is frequently the person in the hospital most qualified to start and maintain a patient properly on inhalation therapy. I have been told that there is sometimes a friendly competition between the therapist and the anesthesiologist to see who can respond most quickly to a call for a critical patient! Like the pharmacist the therapist is frequently in a position to act as a therapeutic consultant to the physician.

Inhalation therapy is achieving departmental status in some of our hospitals. It is sometimes allied with, or a part of, central supply and through the latter may be associated with pharmacy. In addition to providing the direct inhalation service to patients, the department is responsible for the maintenance of inhalation and allied equipment and supplies. Without the services of experts in this field, the hospital can suffer much economic loss through lack of maintenance of this equipment and more important, it will not be available when needed.

I believe the hospital pharmacist can be of invaluable assistance to the inhalation therapist in his service to the patient with pertinent pharmaceutical information and adequate supplies of the latest preparations used in inhalation therapy.

Now that the holidays are over and a new calendar year is starting we can get going on many of the activities we keep putting off. Are we going to have time this month to do all the things we kept delaying "until after the first of the year"?

Just a plug for my own chapter: The Southern California Society of Hospital Pharmacists, over 150 members strong, looks forward to a banner year under its new President, Wendell Hill, Chief Pharmacist, Orange County Hospital. We hope to accomplish a number of projects—getting a hospital pharmacist appointed to the State Board of Pharmacy, closer liaision with the state and local pharmaceutical associations and the county medical society, student recruitment, and most important—good meetings.

JACK S. HEARD

News

Lederle Award Presented

H. S. Carlin, Chief Pharmacist of Colorado General Hospital, Denver, recently received, on behalf of the hospital pharmacy, the Lederle Laboratories award for meritorious community service through pharmacy. The award, presented by J. C. Scheve, Rocky Mountain Regional Manager, Lederle Laboratories Division, American Cyanamid Company, was made after the pharmacy had filled its millionth outpatient prescription.

H. S. Carlin, Chief Pharmacist at Colorado General Hospital, Denver, receives on behalf of the hospital pharmacy the Lederle Laboratories Award of meritorious community service through pharmacy

Lederle citations are awarded to pharmacies which have reached or surpassed the million prescription mark. They recognize the contributions of pharmacists to the public health of their communities "in association with physicians and other members of the healing professions."

AIHP Issues New Slide Talk

"The Great Pharmacist-Chemist Carl Scheele" will come before audiences of laymen and pharmacists through an address with 20 slides (2 x 2), just issued by the American Institute of the History of Pharmacy for presentation locally by pharmacists. Prepared with the collaboration of George Urdang and Ernst W. Stieb, the slide-lecture tells in word and picture something of the life and work of the Swedish chemist Scheele, who is sometimes referred to as "the greatest pharmacist of all time." It touches the highlights of the activities of the man who discovered oxygen (before 1773), the fruit acids, tungsten, molybdenum, and glycerin.

The talk—which takes about 25 to 30 minutes to present—is suitable for showing to pharmacy groups, high-school science clubs, and laymen's service clubs. The text may be edited easily to conform to the style of the particular speaker or the comprehension of the particular audience.

The 20-slide talk with text, based on Urdang's biography of Scheele, is loaned to Institute members* without charge, or may be purchased. The Institute's address is 356 Chemistry Building, Madison 6, Wisconsin.

Hospital Pharmacy Represented at St. John's Congress

The Arrangements Committee for the Second Annual Pharmacy Congress to be sponsored by St. John's University College of Pharmacy on March 17, 1960 at the University campus in Jamaica, N.Y., has announced the program for the affair. The format will be similar to last year's agenda which was so well received and will consist of four separate panels to be held simultaneously on Community Pharmacy, Hospital Pharmacy, Industrial Pharmacy and Medical Detailing.

The Committee has also announced that it has secured the services of four individuals prominent in the field who will moderate the panels and assume the responsibility for arranging the individual sessions.

Calvin Berger, noted community pharmacist and former President of the American College of Apothecaries, will direct the Community Pharmacy section; Louis V. Clemente, Director of Sales, Northeast Region, Eli Lilly Company, will act as Chairman for the Medical Detailing section; Arthur W. Dodds, Chief Pharmacist of the United States Public Health Service Hospital in Staten Island, will arrange the section on Hospital Pharmacy; and Dr. Rudolph H. Blythe, Director of Pharmaceutical Research for Smith, Kline and French Laboratories, will chair the Industrial Pharmacy section.

► COMMANDER ALFRED ROSENBERG of the United States Public Health Clinic in New York addressed the senior class of St. John's University College of Pharmacy at a December meeting, according to an announcement by Dr. Andrew J. Bartilucci, Dean of the College of Pharmacy. Commander Rosenberg spoke on "The Opportunities in the United States Public Health Clinic in New York."

In his talk, Commander Rosenberg outlined the organizational make-up of the Public Health Service and enumerated career possibilities within the Service.

*Note: Membership in the American Institute of the History of Pharmacy is open to pharmacists. The membership fee is five dollars annually.

Sister Berenice Appointed to Policy Committee

Sister Mary Berenice S.S.M.

Sister Mary Berenice, S. S.M., St. Mary's Hospital, St. Louis, Mo., has been appointed the Catholic Hospital Association's representative to the Policy Committee of the Division of Hospital Pharmacy of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. Sister Berenice is well known to the members of the SOCIETY, having served as ASHP Treasurer and a member of the Executive Committee for a number of years.

Other members currently serving on the Policy Committee are William S. Apple and Robert P. Fischelis, representing the American Pharmaceutical Association; Robert R. Cadmus representing the American Hospital Association; and Vernon O. Trygstad, Don E. Francke, Robert C. Bogash, and Leo F. Godley, representing the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS.

► HOSPITAL PHARMACISTS representing the Southern California Society of Hospital Pharmacists, recently met with the Southern California Chapter of the American Association of Inhalation Therapists. Of particular interest to hospital pharmacists is the use of pharmaceutical preparations in inhalation therapy. The Association is sponsored by the American College of Chest Physicians and the American Society of Anesthesiologists.

Legal Division Established by A.Ph.A.

Pharmacist-Lawyer Raymond J. Dauphinais has recently been appointed Director of a new Legal Division established by the American Pharmaceutical Association as an integral part of the Association Headquarters Staff in Washington, D. C.

The announcement was made today by Dr. William S. Apple, Secretary and General Manager of the American Pharmaceutical Association. The A.Ph.A. Legal Division, Dr. Apple indicated, will make it possible for the Association to more effectively inform its membership about legislation and regulatory matters concerned with professional services, drug distribution, and public health. Special studies undertaken by the Legal Division will facilitate the development and implementation of Association policy in these fields.

Mr. Dauphinais, who will assume his new position on February 1, 1960, holds the degree of B.S. in Pharmacy from the University of Illinois and the LLB. from the University of Florida School of Law. Under the direction of the late Charles Wesley Dunn, Mr. Dauphinais received the LL.M. (Trade Regulation) and completed additional study in food and drug law at the New York University Graduate School of Law.

The Director of the new A.Ph.A. Legal Division was the American Pharmaceutical Manufacturers' Association's Fellow in food and drug law during 1955-56. He received the American Jurisprudence Award for Scholarship in constitutional law at the University of Florida School of Law, and in 1956 received the Food Law Institute's award for original research in food and drug law.

Mr. Dauphinais has served as Assistant Professor of Pharmacy at the University of Connecticut School of Pharmacy since February 1957, and previously held teaching positions at the Columbia University College of Pharmacy and the University of Florida College of Pharmacy. He is a registered pharmacist in Florida and Illinois, a member of the Florida Bar, and has engaged in the practice of retail pharmacy, hospital pharmacy, and law.

New Product Reporting Service

Information on new product introductions by ethical pharmaceutical manufacturers in the U. S. is available in a service known as *pharmIndex*. This is a twice-monthly reporting service on new prescription specialties. According to the publisher, this makes available product-information that is up-to-date, complete as to product data, full coverage of manufacturers, and cumulative generic, therapeutic, tradename and manufacturer indexes. The publisher is Wm. C. Felter, Box 1029 Federal Station, Portland 7, Oregon, former editor and publisher of Pacific Drug Review.

According to a release on the service, in the last six months of 1959, a grand total of 306 new ethical pharmaceutical specialties were introduced to the U. S. pharmaceutical and medical professions. This is an annual rate-of-introduction exceeding 600 products a year—fifty percent higher than previous industry estimates. The new higher figure is based upon listings in *pharmIndex*, which has just completed its first full year of publication. Featuring coverage of the entire field of pharmaceutical manufacturing—small firms as well as the "majors"—*pharmIndex* reported 307 new products in its issues from July through December, 1959.

The above figure represents *new products only*, not including new dosage forms, strengths, packages and other changes in already-existing products. Of these latter, *pharmIndex* reported 157 new dosage forms and strengths, plus more new packages, name changes, formula changes, prices, etc., in the last six months of the year.

SELECTED PHARMACEUTICAL ABSTRACTS

and summaries of other articles interesting to hospital pharmacists

edited by CLIFTON J. LATIOLAIS, HENRY J. DEREWICZ *and* LEO F. GODLEY

BISULFITE INCOMPATIBILITIES

Higuchi, T. and Schroeter, L.: Reactivity of Bisulfite with a Number of Pharmaceuticals, J. Am. Pharm. Assoc., Sci. Ed. 48:535 (Sept.) 1959. (School of Pharmacy, University of Wisconsin, Madison, Wis.)

Bisulfite is an antioxidant widely used in many pharmaceutical preparations; however, the compound undergoes reaction with a number of pharmaceuticals with reduced stability. It has been reported that dilute sulfite compounds interact with aromatic nitro compounds. Thiamine cleavage has been demonstrated. Recent reports of the degradative route of epinephrine with bisulfite have resulted in the present investigation on epinephrine and other types of drugs exhibiting close or distant similarity to epinephrine. The experimental method is described.

The loss of optical activity of epinephrine that occurs simultaneously to epinephrine and bisulfite loss strongly suggests that the asymmetric secondary alcohol carbon of epinephrine is the reactive site of reaction to a sulfonic acid derivative. Kinetic evidences indicate a reaction of the second order which is pH dependent. Under the conditions studied, no reactions were detected between bisulfite and ephedrine and analogs, the dihydroxybenzenes, phenylephrine, *p*-hydroxytoluene, *p*-methoxybenzyl alcohol, methyl-*p*-hydroxybenzoate, *m*-hydroxybenzyl alcohol, *p*-aminobenzoic acid, 4-aminosalicylic acid, salicylamide, tartaric acid, and starch. Detectable reactions were found with *p*-methyl-aminoethanol phenol, N-methylepinephrine, N-acetylepinephrine, the ortho and para isomers of hydroxybenzyl alcohols, *p*-aminobenzyl alcohol, salicyl alcohol, and chloramphenicol.

These findings indicate that the epinephrine-bisulphite reaction involves the *p*-hydroxybenzyl alcohol moiety of epinephrine as the active portion. Both of the para and ortho hydroxybenzyl alcohol derivatives react to form corresponding sulfonic acid derivatives. Amino groups, which are para or ortho to benzyl alcohol, activate the alcohol portion by their contributing quinoid resonance. *p*-Nitrobenzyl alcohol derivatives undergo similar reactions as epinephrine but appear to be more complex.

NORMAN HO

COLORING OF MERCURIC CHLORIDE SOLUTIONS

Further Notes on the Coloring of Mercuric Chloride Solutions, Steel, K. J., Pharm. J. 129:253 (Oct.) 1959.

In a previous article, attention was drawn to the incompatibility of mercuric chloride with methylene blue, and the use of indigo carmine or tryptan blue for coloring mercuric chloride solutions was suggested as being more suitable. A brief survey has been made of the coloring agents used in various formulae for mercuric chloride solutions and results of this survey are presented. Results indicate that sulphan blue may be a suitable coloring agent for mercuric chloride solutions provided such solutions are protected from light and not stored at an elevated temperature. Exposure to light or storage at 37°C. caused a change in color from blue to greenish. Sulphan blue has been reported to undergo a similar color change in the presence of potassium chlorate and phenol on exposure to light. The more rapid incompatibility produced upon the addition of methylene blue to mercuric chloride solutions containing sodium chloride does not support the theory that the reaction is due to simple ionization of the mercurial compound. The nature and mechanism of the incompatibility remain obscure but as it was possible to obtain a reaction between mercuric acetate or oxycyanide and methylene blue, the validity of Wilson's theory that the reaction between mercuric chloride and the dye was due to "salting-out" is contradicted. Saline solutions of the three mercuric salts may, however, be suitably colored with indigo carmine, sulphan blue or trypan blue.

HENRY J. DEREWICZ

CHLORAMPHENICOL STABILITY IN BUFFERED SOLUTIONS

The Stability of Chloramphenicol in Buffered Solutions, Broadhurst, N. and Wright, S. E., Australasian J. Pharm. 40:106 (1959).

The authors evaluated the stability of chloramphenicol in solution, varying the pH, the buffer used, the concentration of chloramphenicol, and the method of sterilization.

Using a borate buffer at a pH of 6, 7, and 8, the authors found that the percentage of decomposition was greatest at pH 8, less at pH 7, and least at pH 6. This relationship applied whether the solution was autoclaved at 115° C. for 30 minutes or heated at 100° C for 30 minutes. Decomposition was much greater with autoclaving than with boiling. For example, at a pH of 8, the autoclaved solution of a 0.5 percent concentration showed a decomposition of 22 percent while the boiled solution showed a decomposition of 7 percent. For the same solution at a pH of 6, the decomposition was 5.2 and 3.2 percent, respectively. A solution having a concentration of 0.25 percent and a pH of 6, after boiling, showed a decomposition of only 1.2 percent.

In a comparison of vehicles, the authors reported that a 0.25 percent solution of chloramphenicol boiled at 100° C. for 30 minutes showed a decomposition of 5.2 percent at a pH of 6 in a phosphate buffer, of 1.6 percent at a pH of 7 in distilled water, and of 1.2 percent in a borate buffer at pH 6.

It was concluded that chloramphenicol should be dispensed in a borate buffer at a pH of 6 and should be sterilized by heating at 100° C. for 30 minutes. The following formula was suggested:

Chloramphenicol	0.50 Gm.
Sodium Borate	0.15 Gm.
Boric Acid	4.20 Gm.
Preservative, q.s.	
Distilled Water, to make	100.00 ml.

The chloramphenicol should be dissolved in the buffer solution at 95-98° C. and then cooled quickly.

ABST. FROM AM. J. PHARM. *131:228* (JUNE) 1959.

ADSORPTION OF ODOROUS MATERIALS

Studies on the Adsorption of Odorous Materials II, Surface Potential Changes Due to the Adsorption of Alcohol Vapors, Kopplin, J.O., Eaton, J.R., Christian, J.E., J. Am. Pharm. Assoc., Sci. Ed. 48:521 (Sept.) 1959. (Electrical Engineering and Pharmacy Departments, Purdue University, Lafayette, Ind.)

Because current opinion is that physical rather than chemical processes are critical in olfactory stimulation and because of interest in the possible development of an objective instrument for the measurement of odor, the normal aliphatic alcohols were studied as odorous air stream contaminants. The changes in surface potential caused by the adsorption of the alcohols are presented. It was found that equal concentrations of the different alcohols caused different changes in the surface potential of a distilled-water surface, that the minimum concentrations detectable by the human nose can be determined by measurement of the surface potential changes, and that the relationship between the surface potential changes and the chain length of the alcohols is analgous to certain reported relationships between olfactory stimulation and chain length of the same vapors. These results indicate certain analogies between the changes in surface potential and the olfactory stimulation caused by some vapors, but do not imply that odor has been measured by electrical-mechanical means. However, the results do indicate that there is a need for further research regarding surface phenomenon to try to learn more about the physical properties of adsorbate molecules.

WILLARD HARRISON

DUAL-CONTROLLED AUTOCLAVE

Protective Effects of Air Under Pressure on Certain Pharmaceuticals During Steam Autoclaving, Lockman, L., Jacoma, D. and Eissman, P., J. Am. Pharm. Assoc., Sci. Ed. 48:541 (Sept.) 1959. (Research Department, Ciba Pharmaceutical Products, Inc., Summit, N. J.)

The expansion of collapsible tube and bursting at the crimp end, and the loss of solution from screw-capped containers are problems encountered in the steam sterilization of such products. This is due to the pressure differential in the container and in the sterilizing chamber, particularly during the cooling phase of the sterilization process.

To overcome this problem, a dual-control autoclave was designed in which temperature and pressure could be independently controlled. The autoclave can automatically maintain the desired temperature and pressure during the sterilizing cycle and adjust the introduction of sterile air to the gradual exhaust of steam at a preset rate during the cooling phase.

Formulations of jellies in tubes and ophthalmic solutions in screw-cap, glass containers were subjected to various combinations of temperatures and pressure to determine the sterilizing effectiveness of the dual-control autoclave and to determine the ability of the tubes and glass containers to withstand any physical changes under these conditions. It was found that the physical state of the tubes and glass containers were unaltered and that sterility was maintained at the range of 95°C. and 10 p.s.i. to 115°C. and 30 p.s.i. for a period of 30 minutes. Furthermore, measurements of temperature of the tubes, bottle content and autoclave chamber reported a lag in the rise and fall of temperature in the tubes and bottles as compared with that in the chamber. The temperature lag was greater for the bottle contents than for the tube contents; this can be explained by the difference in the thermal conductance of the two containers.

NORMAN HO

FORMULATION OF LIQUEFIED PHENOL

Phase Equilibria of Phenol-Water Mixtures and the Formulation of Liquefied Phenol, Mulley, B. A., Drug Standards 27:108 (July-Aug.) 1959. (Chelsea College of Science and Technology, London.)

The author of the article suggests a new formulation for liquefied phenol which would have a number of advantages over those mixtures now in common use. As a result of investigation with several phenol-water mixtures, a convenient formulation for a single phase phenol-water mixture was found to be 80% w/v corresponding to about 76.1% w/w. The main advantage of this mixture is the fact that it enables weights of phenol to be obtained directly from a volume of the solution. Previous formulations were not satisfactory from this point of view.

THOMAS E. ARKINSON

TABLET COATING WITH A RESIN

Tablet Coating with a Polyethylene Oxide Water Soluble Resin, Blaug, Seymour M. and Gross, Milton R., Drug Standards 27:100 (July-Aug.) 1959. (State University of Iowa, College of Pharmacy, Iowa City, Iowa.)

A procedure for coating of tablets using the water-soluble resin Polyox WSR-301 is described. This high molecular weight resin in combination with polyethylene glycol 400 produced a smooth uniform type of tablet coating which is easily applied and which requires little experience in tablet coating procedures. Disintegration times obtained are well within the U.S.P. limits. The coat is nonhygroscopic and displays a marked resistance to chipping and cracking. Among the advantages described are the factors of low solids content, as well as reproducibility of results. The coating is non-caloric and sugar free.

THOMAS E. ARKINSON

CHROMATOGRAPHY OF TISSUE AMINES

Paper Chromatography of Some Tissue Amines, West G. B., J. Pharm. and Pharmacol. 11:595 (Oct.) 1959. (Department of Pharmacology, School of Pharmacy, University of London, Brunswick Square, London, W.C. 1).

When solutions of adrenaline, novadrenaline, histamine, 5-hydroxytryptamine and related amines in trichloracetic, trifluoracetic or picric acid are chromatographed in various organic solvent systems, the active material divides into two areas. If a basic amino acid is included in the solution before chromatography, the separation becomes more complete. It is suggested that the second area consists of a loose complex between the amine and the corresponding acid. When solutions of the amines in hydrochloric, acetic or oxalic acid are chromatographed, the active material resides only in one area.

AUTHOR'S SUMMARY

DRUG RELEASE FROM TIMED RELEASE TABLETS AND CAPSULES

A Suggested in Vitro Procedure for Measuring the Rate of Drug Release from Timed Release Tablets and Capsules, Vliet, Elmer B., Drug Standards 27:97 (July-Aug.) 1959. (Abbott Laboratories, North Chicago, Ill.)

The author describes a method for measuring the timed release rate of tablets and capsules. The procedure involves utilization of apparatus which is somewhat modified from that described in official U.S.P. disintegration tests. It is believed that the methods and procedures described represent a useful and more convenient routine control on products of this type. The effectiveness of timed release products is dependent upon many different disintegration principles, hence, the proposed methods may not be useful in every case.

THOMAS E. ARKINSON

STABILIZERS FOR ASCORBIC ACID SYRUPS

A Note on the Comparison of Three Stabilizers for Ascorbic Acid Syrups, Shah, R. H. and Huyck, C. L., Drug Standards 27:110 (July-Aug.) 1959. (Department of Industrial Pharmacy, St. Louis 10, Mo.)

Ascorbic acid syrups are oxidized if stored on contact with oxygen. This investigation employed the use of three possible stabilizing agents in an attempt to develop a stable syrup of ascorbic acid. The agents used were (a) sodium bisulfite, (b) propylene glycol and sorbitol, and (c) cyquest 40 sequestrant 40%, which is a 40% tetrasodium salt of ethylenediamine tetraacetic acid. Stability of the syrups under investigation was studied at different temperatures, and the samples were assayed over a period of five weeks. Of the three groups tested, the most stable formulation contained the agents from group (b) above.

THOMAS E. ARKINSON

FILTRATION OF BACTERIOPHAGE

A Study of the Filtration of Bacteriophage, Jordana, R., Applied Microbiol. 7:239 (July) 1959. (Institutes of Microbiology).

A study was performed in order to determine the effect of filters upon the removal of filterable phage from bacterial suspensions. Overnight suspensions of *Bacillus polymyxaphage* or *Escherichia coli* phage were used as the sources. A comparison was made of the number of phages in the original suspension and the number in the filtrate after filtration. Filters used in the study were Chamberland Candles 5L3 and 5L5, sintered glass plates 5/3 from two sources, and Seitz EK pads from three sources. Filtration produced the following results:

a. A preliminary vacuum filtration of 10 ml. of phage suspension through each of the filters showed that adsorption was negligible for sintered glass plates and Chamberland filters but quite pronounced for Seitz pads. Varying the pH of the suspensions produced negligible adsorption for the sintered glass and Chamberland filters.

b. Acid pH values caused complete absorption with Seitz EK pads, although in the alkaline range, a small number of particles passed through. In addition, the use of small surface area filters of the Seitz type allowed more phage particles to pass through and increasing the volume of solution filtered increased the number of particles passed through. However, acid suspensions yielded less particles in the filtrate than did alkaline suspensions.

c. Different sources of vacuum, which produced differences in negative pressure and the rate at which the maximum was attained, produced differences in adsorption. Also, lower filtration pressure differentials produced greater adsorption than higher pressure differentials. Estimates of maximum yield of particles in the filtrates under a constant vacuum of 650 mm. of mercury over the pH range of 5.9 to about 7.5 showed that the pH of maximum yield was about 6.85. When 50 ml. of suspension was filtered, over 95% of particles were obtained in the filtrate, whereas total adsorption occurred when 10 ml. of suspension was filtered through an identical filter at a pH of 5.9.

HENRY J. DEBEWICZ

CLOSURE DEVELOPMENTS

Closures Today and Tomorrow, Emanuel, E. C., Drug and Cosmetic Industry 85:767 (Dec.) 1959. (Armstrong Cork Company.)

In 1926, the trend away from the use of natural corks started. Tin and aluminum screw caps were inaugurated into use as well as a new material known as bakelite, a thermosetting, molding compound made from a phenol-formaldehyde resin. The molded cap became practical when glass manufacturers produced screw finished containers within reasonable tolerance limits, so that the cap would fit the containers. As the use of more molded caps progressed, various problems arose such as strength of a cap to withstand suddenly applied capping pressures; and the effect of moisture and humidity on the caps. Prior to 1938, only thermosetting materials were available; but the development of polystyrene molding compounds in that year started the process of injection molding. Polystyrene has excellent resistance to inorganic acids and alkalies so that its use has been employed for strong mineral acids and other types of closures which required a resistant compound. Modification of polystyrene and other thermoplastic materials has been a continuous process and advances will continue to be made in the closure field to meet new requirements as they arise.

ROBERT P. MCMAHON

EMETINE ASSAY

Colorimetric Estimation of Emetine in Ipecacuahna, Sarin, J.P.S., Nandi, R. C. and Ray, G. K., Indian J. Pharm. 21:308 (Nov.) 1959.

A simple colorimetric method for the estimation of emetine in ipecacuahna is described. It was found that emetine forms, with methyl orange, a chloroform soluble complex, the color intensity of which was found to be a direct measure of the emetine content at a definite pH. It was found that in concentrations of 5 ug to 20 ug of emetine the complex obeyed Beer's Law. The color is stable only between pH 4.2 and 5.0 so an acetate buffer (pH 4.6) is used as the diluent. Readings must be taken soon after color development because the color intensity deteriorates fast after five minutes separation from the reaction tube. Methods are described for estimating the emetine content in powdered ipecacuahna roots as well as in the tincture of ipecacuahna.

WILLARD L. HARRISON

SPECTROANALYTICAL TECHNIQUES

Instrumental Examination of Aromatics, Theimer, Ernest T., Drug and Cosmetic Industry 85:754 (Dec.) 1959. (Van Ameringen-Haebler Division, International Flavors & Fragrances, Inc.)

Application of the various spectroanalytical techniques—ultraviolet, infrared, mass, nuclear magnetic resonance, and the separation technique of vapor phase chromatography—to the structure-proof of a number of fragrance materials is presented. A mixture of primary terpene alcohols of known composition is separated and analyzed and the structures of geraniol and citronellol are derived using these techniques alone. Mass spectra of the terpene alcohols, as obtained with the newly developed Time-of-Flight mass spectrometer, are compared with those from a space magnetic type instrument. Special emphasis is given to a discussion of the data available from a careful analysis of nuclear magnetic resonance spectra of the same terpene alcohols.

ROBERT P. MCMAHON

FLAVORING ANTIBIOTICS

The Flavoring of Antibiotic Products, Spiegel, A. J., and Noseworthy, M. M., Drug and Cosmetic Industry 85:749 (Dec.) 1959. (Chas. Pfizer & Co.)

The various problems encountered in the flavoring of antibiotic products, as well as considerations to be dealt with in an attempt to provide maximum acceptability, are discussed. Factors such as age play an important part in the selection of an appropriate flavor. Another important consideration in the use of flavors is the taste characteristic of the drug to be masked or blended. These taste characteristics involve initial, intermediate, and aftertaste; and for antibiotics all these test groups are experimented with until a satisfactory result is obtained. The product is then subjected to taste panels. Three types of panels are employed; individuals with a high taste sensitivity, an average cross-section consumer panel, and a taste panel consisting of 25 children. A mean rating is obtained from all the results which are scored on a numerical point basis. The major problem of flavoring antibiotics is the characteristic bitterness associated with this class of drugs and each antibiotic presents a separate problem which must be handled individually.

ROBERT P. MCMAHON

TOXICITY OF DRUG SOLVENTS

Toxicity of Three Drug Solvents, Davis, Kent J. and Jenner, Paul M., Toxicology and Applied Pharmacology 6:576 (Nov.) 1959. (Division of Pharmacology Bureau of Biological and Physical Sciences, Food and Drug Administration, United States Department of Health, Education, and Welfare, Washington, D.C.)

Solvent toxicity becomes an important consideration in toxicologic experiments with those relatively insoluble, slightly toxic, drugs which require administration of large volumes of dilute solution. The three solvents tested by intraperitoneal injection in mice were N, N-dimethylforamide which was administered undiluted, fifty percent solution of N, N-dimethylacetamide, and propylene glycol which was administered undiluted. N, N-dimethylforamide was approximately ten times as toxic, and N, N-dimethylacetamide (in fifty percent aqueous solution) was approximately three and one-half times as toxic as propylene glycol. The LD_{50} values were respectively 1122, 3236, and 11,400 mg./Kg.

ROBERT P. MCMAHON

CURRENT LITERATURE

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

ADMINISTRATION

—Costs

Vance, Joe: Probe of Drug Costs, The, *Southern Hospitals* 28:56 (Jan.) 1960.

—Policies

Latiolais, C. J.: Hospital Pharmacy Practice—New Horizons Beckon, *Hospitals* 34:61 (Jan. 1) 1960.

—Salaries

Anon: Duties, Salaries of Pharmacists Surveyed, *Hospitals* 34:64 (Jan. 1) 1960.

CIVIL DEFENSE

Gibson, L.: National Health Conference on Civil Defense, *Hosp. Pharmacist* (Canada) *12*:267 (Nov.-Dec.) 1959.

EQUIPMENT AND APPARATUS

Swallow, W.: Sensitivity and Tolerances of Pharmaceutical Balances, The, *Public Pharmacist* (Great Britain) *16*:242 (Nov.) 1959.

Wood, D. G.: Simple Tube Folder, A, *Public Pharmacist* (Great Britain) *16*:233 (Nov.) 1959.

LAWS AND REGULATIONS

McMurray, R. D.: Law of Pharmaceutical Advertising, The, *Drug & Cosmetic Ind. 85*:752 (Dec.) 1959.

MANUFACTURING AND CONTROLS

Teare, F. W.: Quality Controls for Hospital Manufacturing, *Hosp. Pharmacist* (Canada) *12*:269 (Nov.-Dec.) 1959.

Spiegel, A. J. and Noseworthy, M. M.: Flavoring of Antibiotic Products, The, *Drug & Cosmetic Ind. 85*:749 (Dec.) 1959.

PUBLIC RELATIONS

Griffenhagen, George: Pharmacist and Public Relations, The, *Hosp. Progress 41*:74 (Jan.) 1960.

STERILIZATION

Kahn, Sidney: Standardization and Use of Germicides, The, *Hosp. Management 89*:88 (Feb.) 1960.

Royce, Alex: Modern Sterilizing and Aseptic Technics, *Public Pharmacist* (Great Britain) *16*:235 (Nov.) 1959.

DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

► THE FOLLOWING MONOGRAPHS and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations. In order to make the material even more valuable, dosage forms and preparations of individual drugs have been added to the monographs. These dosage forms and preparations were not taken from material published in the *Journal of the American Medical Association* by the Council on Drugs; rather, they were obtained from such manufacturers' brochures, news releases, etc., which were available to us at the time of publication. An attempt has been made to make the list of dosage forms as complete as possible. However, no guarantee can be made that the list of preparations is complete and it is suggested that hospital pharmacists consult manufacturers' releases for additional dosage forms and preparations.

The issues of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of the JOURNAL include some of those published in the *A.M.A. Journal* for October 24 and November 7, 14 and 21.

Notice

New and Nonofficial Drugs 1959 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1959 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to January 1, 1959. The indexes listed below contain those drugs evaluated and published between December 20, 1958 and November 21, 1959.

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TO DRUGS EVALUATED IN THIS ISSUE

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TO EVALUATED DRUGS AND ARTICLES IN THE FEBRUARY, 1959 THROUGH THE JANUARY, 1960 ISSUES OF THE AMERICAN JOURNAL OF HOSPITAL PHARMACY.

REPORT TO THE COUNCIL

The Council has authorized publication of the following report. H. D. Kautz, M.D., *Secretary*

CURRENT STATUS OF THE THERAPY OF BURNS

Isidor S. Ravdin, M.D., *Philadelphia*

MANY of the most important aspects of the therapy of burns have not changed to any significant degree in the last few years. The need for supportive therapy of a general character, gentleness in the handling of the patient, and exacting cleanliness in the handling of the burned patient are just as fundamental today as they were before the days of chemotherapy, of transfusion, and of fluid and electrolytes. These fundamental principles apply to the patient as a whole, as well as to the local wound. They, very likely, outweigh recent contributions which have been made in the care of the burned patient.

General Considerations

Significant strides have been made in the treatment of shock with the greater use of blood, plasma, and, at times, plasma expanders. Significant progress has been made in the prevention of electrolyte imbalance, its recognition, and correction. Septicemia, the greatest cause of death in the salvable burned patient, has been curtailed by the judicious use of antibiotics. It is important, however, to point out that the routine prophylactic use of systemically administered antibiotics is probably contraindicated except in the very severe burns. When antibiotics are indicated, they should be changed every few days to minimize the development of resistant strains of organisms. When staphylococcic infection occurs, the strains should be rapidly determined, and the antibiotics used should be those to which these strains are sensitive. The use of cortisone (Cortisone, Cortogen, Cortone) acetate and corticotropin (Acth, Acthar, Corticotropin) has been discontinued almost completely.

It should be pointed out that the careful use of specifically indicated antibiotics may be lifesaving in patients who have developed septicemia but that, in the local care of the burn wound, antibiotics have contributed very little. Surgical cleanliness in the care of the wound is more important than the use of antibiotics to control surface infection of the burned area, where infection has taken place because of inadequate cleanliness.

John Rhea Barton Professor of Surgery, Hospital of the University of Pennsylvania Department of Surgery.

Specific Measures

Widespread claims have been made for a variety of locally applied agents concerning their ability to accelerate nature's processes of healing; however, the most exacting studies have failed to fulfill the claims made for any of these agents. After careful study, the innumerable substances which have been advocated for local use have proved to be of little practical value. In fact, many of the agents which have been used to promote healing have been shown to be detrimental to epithelization.

Enzymatic débriding agents have been advocated by several investigators, but, in spite of impressive laboratory work, they have not proved to be very effective in man. The best method of cleaning the burned area, if this is necessary, is still by washing with surgical soap and sterile water or physiological saline solution. The best débridement is still achieved by time or the surgeon's scalpel, and the best dressing is still a fine-mesh gauze lightly impregnated with an innocuous bland ointment.

The only worthwhile place for a specialized burn ointment (if such an ointment exists) seems to be on a small superficial burn for the immediate relief of pain. Even so, burn wounds are seen daily which have had no mechanical cleansing and which are badly infected, in spite of the generous application of some proprietary ointment. History has repeated itself over the centuries.

Clinical studies have shown clearly that, in third degree burns, rapid healing is best obtained if the granulating surface and surrounding skin are kept meticulously clean with soap and water, plus the frugal use of ether or benzene for the removal of keratin scales and macerated tissues. Skin grafting is faster than any known therapeutic agent in providing cover-

age for areas of deep burns, reducing the bacterial flora of a wound, and restoring the critically burned patient to good health. Frequent blood transfusions, light safe anesthesia, and nutritional adjuncts given intravenously or orally have added greatly in reaching this goal. The best means of providing adequate calories is by mouth. This method should always be used if possible. Intravenous alimentation should be used to increase oral caloric intake, if this is inadequate.

Progress in the treatment of burn shock has been great, and, if it is treated early, the large majority of severely burned patients can now be brought successfully through this phase of their injury. Several formulas have been proposed as guides for the administration of fluid during the shock phase. At times, too much fluid is given, and pulmonary edema is produced. One cause of overhydration is overestimation of the area burned. Less than the estimated volume of fluid should be given to children, elderly patients, those with serious heart disease, those with respiratory burns, and those with more than 40% of burned body surface. Each patient's response must be closely observed and his therapy adjusted accordingly. The use of an indwelling catheter in the urinary bladder enables one to follow closely the rate of formation of urine and is helpful in judging the adequacy of intake. Urine formation of 25 to 50 cc. an hour is a satisfactory rate, but fluid therapy should not be gauged on this factor alone.

Contrary to the prevailing opinion of a decade ago, it is now believed that large quantities of salt may be necessary in the early phase of treatment because of the rapid fall in the level of serum sodium. Associated with the rapid drop in serum sodium, there is a period of sodium retention usually lasting several days. After the period of retention, the kidneys usually excrete a large amount of fluid and sodium, unless severe renal damage exists. If the salt solution can be given orally, a weaker solution not only is better tolerated but also obviates the necessity of giving the extra water intravenously. The more severely burned patients, however, often cannot tolerate fluids given by mouth.

The rapid loss of plasma from the burned surface and into the tissue beneath the burn has long been recognized, and, until recent years, plasma alone has been considered the proper colloid with which to combat this loss. Recent evidence indicates that whole blood is also needed in burn therapy. Whole blood is needed not only to prevent anemia, long observed to occur several days after burning, but also to replace the red blood cells that are destroyed after burning. Determination of hemoglobin and hematocrit levels gives no indication of this loss and cannot serve as a reliable guide for the volume of whole blood needed.

One of the most striking changes in burn therapy in recent years has been the more frequent acceptance of the open method of treatment. From the reports of several excellent investigators, it appears that the open method can be used with equally good results in some patients. The open treatment is not a treatment of neglect but a method which requires skill and a thorough knowledge of the principles of wound healing. This treatment must not be used for granulating surfaces. Some of its advocates do not advise its use for burns of the flexor surfaces of the neck, for circumferential lesions of the trunk, and for burns on the surfaces of joints of the legs and arms.

General agreement exists that full-thickness burns should be excised and the defect grafted as soon as this is feasible. Early excision and grafting shortens the period of protein loss from burned surfaces, diminishes infection and toxic absorption, and reduces scar formation. Immediate excision and grafting, however, may be prevented by the general condition of the patient, which may make additional trauma too hazardous, and the difficulty of immediately judging the depth of the burn. In burns of limited extent that are obviously full-thickness burns, early excision and grafting is the best treatment. In the patient with extensive burns, the additional trauma of anesthesia and operation may be contraindicated in the early stages of the burn. Excision of dead skin, however, once carried out, will improve the patient's condition at any stage. It is then a question of balancing these two factors with the fact that obvious full-thickness burns should be excised and grafted as soon as the patient can stand the operation. If the normal skin of the patient is insufficient for grafting or if the added trauma of taking a graft is felt to be unwarranted, homologous skin can be used to cover the wound as a temporary expedient. Because grafted skin is usually inferior to superficially burned skin that has regenerated, the ultimate result may be better if in questionable cases, time is given for demarcation before skin is excised.

The early hope that corticotropin and cortisone might effect a permanent "take" of homologous skin has been shown to be ill-founded. In extensive burns, especially in children, the temporary covering of the wound with homologus skin may be lifesaving, even though subsequent replacement with the patient's own skin is necessary.

Comment

It is hoped that in the future we can look forward to better ways of distinguishing superficial burns of first or second degree from deep burns of third degree. It is hoped, too, that we will achieve a better understanding of the "toxic" phase of a burn. Perhaps we shall find better débriding agents with a higher specificity for necrotic tissue, and, perhaps, better agents to stimulate epithelization. In spite of the development of many potent antibiotics, sepsis continues to plague the severely burned patient. All too frequently the patient survives burn shock, the toxic manifestation of the injury, and the early phases of treatment, finally dying from sepsis after several weeks. Local agents to control pain are no longer used. Gentleness in the care of the patient and early removal of necrotic skin, with early grafting, provide the best means of making the patient comfortable.

J.Am.Med.Assoc. 171:182/1357 (Nov. 7) 1959.

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based upon available evidence and do not in any case imply endorsement by the Council.

H. D. KAUTZ, M.D., *Secretary*

Chloroquine (Aralen) Phosphate

Additional Uses of

The Council has reviewed the available evidence concerning the use of chloroquine phosphate in the treatment of lupus erythematosus and rheumatoid arthritis. The use of the drug in the treatment of malaria and systemic amebiasis is currently described in New and Nonofficial Drugs.

The value of chloroquine phosphate in chronic discoid lupus erythematosus is now generally accepted. It appears to be equally as effective as quinacrine and considerably less toxic. About 60 percent of patients exhibit complete remission or marked improvement characterized by regression of skin lesions and increased tolerance to light. Progress is most rapid during the first month of treatment but may continue at a more gradual rate for several weeks thereafter. About one-third of the patients who respond relapse when administration of chloroquine phosphate is discontinued, but many of these will again respond to readministration of the drug.

The status of chloroquine phosphate in the disseminated or systemic form of lupus erythematosus is controversial. The drug must not be relied upon in the acute form of the disease. In the subacute and chronic phases, some investigators have reported favorable results, whereas others have expressed the opinion that the drug aggravates the symptoms and is contraindicated. Large doses are said to be especially likely to cause a flare-up of constitutional symptoms. The administration of small doses of chloroquine phosphate to patients receiving adrenocorticosteroids has been reported to produce favorable results and to make possible a reduction in dosage of the steroids.

Chloroquine phosphate frequently produces some symptomatic relief in rheumatoid arthritis and thus may be a useful supplement to the basic therapeutic regimen of rest, physiotherapy, and diet.

In this condition the response is typically delayed; although subjective relief may be reported within 2 weeks after administration is begun, objective signs of improvement are ordinarily visible only after 6 weeks to 3 months, and maximum benefit only after 6 to 12 months. Any improvement produced is generally maintained with continued treatment, although many patients continue to exhibit minor exacerbations and remissions. As might be expected, patients with gross joint damage respond poorly; otherwise there is little correlation between the degree of response and the duration and stage of the disease or the severity of the inflammatory process. The sedimentation rate, erythrocyte count, and other laboratory findings may show a little change, even in the presence of clinical improvement. Chloroquine phosphate may be used in conjunction with salicylates, and, when so used, a reduction in dosage of the latter drugs is often possible. Combinations of chloroquine phosphate and adrenocorticosteroids, gold salts, and other antirheumatoid drugs have had only limited trial; the value and possible dangers of such combinations are unknown, but it would seem that drugs with similar side-effects, such as rashes, should be avoided. Patients who have relapsed while on steroid therapy rarely respond to administration of chloroquine phosphate.

The mechanism of action of chloroquine phosphate in lupus erythematosus and rheumatoid arthritis is unknown. It has been suggested, however, that these and other collagen diseases represent hypersensitivity reactions and that chloroquine phosphate suppresses the formation of the antigens responsible for the reactions, whereas adrenocorticosteroids interfere with the reaction after it is established.

Although chloroquine phosphate is well tolerated as used in the treatment of malaria, side-effects occur frequently and are often of considerable severity when it is employed for the treatment of lupus erythematosus or rheumatoid arthritis. About 10 percent of patients with these diseases are unable to tolerate adequate doses. The percentage of patients to whom the drug is acceptable can be increased by starting with very small doses and gradually increasing this dosage. Among the less serious reactions reported are headache, pruritus, visual disturbances, gastrointestinal complaints, and lymphedema of the forearm and hands. Skin reactions occur frequently and include dryness, itching, urticaria, maculopapular eruption, desquamation, exfoliation, increased pigmentation, alopecia, and graying or bleaching of the hair; preexisting psoriasis may become worse. Exposure to the sun or to ultraviolet may severely aggravate the dermatitis. The more severe skin reactions often necessitate withdrawal of the drug. Leukopenia, which has been reported, also requires that administration of the drug be stopped. Temporary blurring of vision due to interference with accommodation has been observed. Corneal changes, such as edema or opacification of corneal epithelium, with or without such symptoms as visual halos or blurred vision, have been noted on slit-lamp examinations. These changes, which may begin several weeks to several years after treatment is begun, are thought to be reversible. Should such changes occur, however, the advantages of discontinuing the drug must be weighed, in each case, against the therapeutic benefits that may accrue from continuation of treatment. Gastrointestinal intolerance, dizziness, and headaches also occur.

All patients receiving chloroquine phosphate should have periodic blood cell counts.

The dose of chloroquine phosphate in chronic discoid lupus erythematosus is 250 mg. per day, administered orally. Treatment may be continued until maximum benefit is obtained. Should relapse occur after the drug is withdrawn, it may again be administered at the same dosage level.

If chloroquine phosphate is tried in disseminated lupus erythematosus, the initial doses should be very small: 25 to 50 mg. given on alternate days. The dosage may be gradually increased in accordance with the patient's tolerance. The use of larger doses initially may precipitate an acute exacerbation of an already critically severe illness.

In the treatment of rheumatoid arthritis, 250 mg. is administered daily as a single oral dose. If no beneficial effects are apparent after 6 to 12 weeks of treatment, it is unlikely that continued administration of the drug will result in improvement, though maximum response may be delayed for six months or more.

If troublesome minor side-effects appear during the treatment of either rheumatoid arthritis or lupus erythematosus, the drug should be withdrawn for a few days and treatment reinstituted at a reduced dosage level. The dose may then be cautiously and gradually increased as the patient's tolerance permits.

Administration of chloroquine phosphate should be stopped immediately, and should not be resumed, if marked leukopenia or severe skin reactions appear.

The Council voted to amend New and Nonofficial Drugs to describe the use of chloroquine phosphate in the treatment of rheumatoid arthritis and lupus erythematosus.

Winthrop Laboratories cooperated by furnishing scientific data to aid in the evaluation of these additional uses of chloroquine phosphate.

J.Am.Med.Assoc. *171*:176/1504 (Nov. 14) 1959.

Ferrous Fumarate

Firon®
Fumiron®
Hemoton®
Toleron®

FERROUS FUMARATE (Ferrous Fumarate, Firon, Fumiron, Hemoton, Toleron) has the empirical formula of $FeC_4H_2O_4$.

Actions and Uses

Ferrous fumarate is an anhydrous salt of a combination of ferrous iron and fumaric acid. It contains 33 percent iron by weight. Ferrous fumarate is employed clinically for the treatment of iron deficiency anemia. Available data, while limited, indicate that the drug is probably as effective for this purpose as other orally administered ferrous compounds. Thus, it may be expected to produce an adequate rise in hemoglobin levels (2 Gm. per 100 cc. in three weeks) and a satisfactory increase in hematocrit (5 percent or more in three weeks) in patients with microcytic, hypochromic anemias due to iron deficiency. Such anemias are commonly seen in infancy or pregnancy in which the demand for hemoglobin is increased or in situations in which there is a deficient intake of iron or an excessive loss of iron as in hemorrhage or heavy menstrual flow. If a satisfactory hematological response is not obtained after a therapeutic trial with the drug, medication should be stopped and other diagnostic measures begun. Failure to respond to hematinic agents may indicate that anemia is not due to iron deficiency, that complicating disease is interfering with the ability of the bone marrow to respond, that there is continuous active blood loss, or that there is impaired absorption of iron. Thus, it is important in all cases to search for the underlying cause of anemia.

The acute toxicity of ferrous fumarate in experimental animals is low. It is also well tolerated clinically, and there is some evidence to indicate that it may be superior to ferrous sulfate or ferrous gluconate in this respect. Thus, occasional patients will experience the gastrointestinal disturbances (anorexia, nausea, vomiting, cramping, diarrhea, constipation) typical of orally administered iron salts. These complaints are generally mild and tend to subside as therapy is continued. In some instances, ferrous fumarate may be used satisfactorily in patients unable to tolerate other orally given preparations. As with all drugs of this class, ferrous fumarate is contraindicated in the presence of peptic ulcer, regional enteritis, and ulcerative colitis. In patients with usual sensitivity to orally given iron salts, preparations which are suitable for parenteral use should be employed. Also,

when the cause of the anemia has been removed, a single dose of parenterally administered iron may be used to replace iron stores, in place of protracted oral therapy.

Dosage

Ferrous fumarate is administered orally. Each 200 mg. of the drug is equivalent to about 65 mg. of elemental iron. For adults, the usual dose is 200 mg. three to four times daily. No data are available to permit dosage recommendations for infants and children.

Preparations

Tablets 200 mg. and 324 mg.

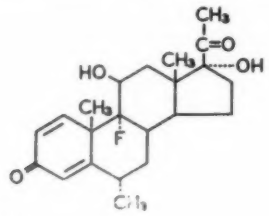
Year of introduction: 1957.

Mallinckrodt Chemical Works cooperated by furnishing scientific data to aid in the evaluation of ferrous fumarate.

J.Am.Med.Assoc. **171:126/1104 (Oct. 24) 1959**

Fluorometholone — Oxylone®

FLUOROMETHOLONE (Oxylone) is 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione.—The structural formula of fluorometholone may be represented as follows:



Actions and Uses

Fluorometholone is a highly potent gluco-corticoid which is used exclusively for its anti-inflammatory effects on the skin. The drug shows a marked specificity of anti-inflammatory action with topical application. Thus, it is approximately 40 times as potent, on a weight basis, as hydrocortisone when applied to the skin but is equipotent with hydrocortisone when administered orally. Because of this greater specificity of local over oral activity and the consequent low doses required for local effects, undesirable systemic hormonal effects due to possible absorption of the steroid from the skin are highly unlikely.

Fluorometholone is effective by topical application for the treatment of acute or chronic dermatoses that have an allergic or inflammatory basis and are associated with pruritus. These include contact dermatitis, atopic dermatitis (including allergic eczema, neurodermatitis, and eczematoid dermatitis), seborrheic dermatitis, pruritus with lichenification, and nonspecific anogenital pruritus. Although no clear-cut superiority has been demonstrated, the results of therapy with fluorometholone have been comparable to those obtained with other steroids known to be satisfactory for these skin disorders. In view of its specificity of anti-inflammatory action when used topically, fluorometholone appears to be well suited for the management of allergic dermatoses.

As with other topically applied steroids, fluorometholone should not be used on infected areas of skin unless appropriate anti-infective therapy is instituted simultaneously. The drug is contraindicated in the presence of tuberculosis of the skin and should not be applied to the areas adjacent to the eye in patients with ocular herpes simplex. There is no evidence of local irritation or sensitivity after the topical use of fluorometholone.

Dosage

Fluorometholone is applied topically. A preparation containing 0.025 percent fluorometholone is rubbed into the involved areas of skin one to three times daily.

Preparations

Cream (topical) 0.025 percent.

Year of introduction: 1959.

The Upjohn Company cooperated by furnishing scientific data to aid in the evaluation of fluorometholone.

J.Am.Med.Assoc. **171:168/1692 (Nov. 21) 1959.**

Heparin Potassium — Clarin®

HEPARIN POTASSIUM (Clarin) is the potassium salt of heparin. The preparation is standardized in terms of the International Unit which represents the activity of 7.7 mcg. (0.0077 mg.) of heparin sodium standard.

Actions and Uses

Heparin potassium is proposed for sublingual administration as an adjunct in the management of atherosclerosis by virtue of its effects on the physicochemical properties of the blood fats; it is not intended for use as an anticoagulant when given by this route. Heparin is a molecule of large size, and little absorption from the buccal mucous membrane is to be expected. At present the evidence is somewhat conflicting, but it indicates that amounts of the drug sufficient to approximate the action of small doses of parenterally injected heparin sodium on the physicochemical state of the blood fats are often, but not always, absorbed from beneath the tongue. Thus, the potassium salt, when given by the sublingual route, may cause the same changes in the physicochemical state of blood lipids as has been previously described for injections of the sodium salt. (See the monograph on heparin sodium, U. S. P., in New and Nonofficial Drugs.) However, there is as yet no convincing objective evidence that heparin, given sublingually, either prevents or ameliorates any manifestation of cardiovascular disease. Hence, the use of heparin potassium in the hope of ameliorating the progress of atherosclerosis must be considered experimental.

In the doses usually employed, heparin potassium has shown no demonstrable effect on clotting time and is believed to be relatively safe for use, from the standpoint of possible adverse effects on blood coagulation.

Dosage

Heparin potassium is administered sublingually. The proposed dose is 1,500 International Units three times a day given after meals.

Preparations

Tablets (sublingual) 1,500 International Units.

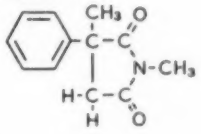
Year of introduction: 1958.

Thos. Lemming & Co., Inc., cooperated by furnishing scientific data to aid in the evaluation of heparin potassium.

J.Am.Med.Assoc. **171:127/1105 (Oct. 24) 1959.**

Methsuximide — Celontin®

METHSUXIMIDE (Celontin) is N,2-dimethyl-2-phenylsuccinimide.—The structural formula of methsuximide may be represented as follows:



Actions and Uses

Methsuximide is an anticonvulsant agent closely related chemically and pharmacologically to phensuximide. The two drugs show a similar pattern of activity in suppressing experimentally induced seizures in animals and both are relatively more effective against convulsions induced by pentylenetetrazole than those produced by electroshock.

In the reported clinical trials, methsuximide reduced significantly the incidence of seizures in about 40 percent of the patients in whom it was used. Approximately 45 percent of the patients with petit mal seizures, 40 percent of those with psychomotor attacks but only 20 percent of those with grand mal epilepsy responded favorably. It provided complete control of seizures in about 15 percent of cases of petit mal and 10 percent of psychomotor attacks.

Approximately 30 percent of patients receiving methsuximide experience undesirable side-effects. In descending

order of recorded frequency these include drowsiness, ataxia or dizziness, gastrointestinal disturbances (including anorexia, nausea, vomiting, constipation, diarrhea), skin eruptions, irritability, psychic disturbances (ranging from slight alterations of mood or personality to occasional acute psychoses), headache, and diplopia or blurring of vision. Fever, hiccough, and severe diaphoresis have been observed in a few patients. In many instances, aside from patients with rash, reduction in dosage results in elimination of the toxic manifestations.

Although it has not been definitely established that methsuximide damages either the kidney or the liver, several reports are suggestive of such damage; therefore, patients receiving the drug should be carefully observed for evidence of renal or hepatic dysfunction. Two patients have developed periorbital edema, associated in one with albuminuria, during methsuximide therapy. Two others have manifested signs suggestive of hepatic dysfunction, including positive cephalin flocculation test, icterus, tenderness in the region of the liver, and spider angiomas. Although examination of the peripheral blood has disclosed no evidence of adverse effects on the hematopoietic tissues, periodic blood studies should be made during therapy.

In chronic toxicity studies in animals, methsuximide was well tolerated; in rats, however, very large doses produced mild to moderate central lobular necrosis and other cytological changes in the liver.

Methsuximide is not the drug of first choice in any forms of epilepsy. It may be effective, however, when other drugs fail. It is most apt to be useful in many cases of psychomotor seizures, which are frequently refractory to other drugs. It may also be tried in petit mal seizures when older, conventional drugs are ineffective or are not tolerated by the patient. Methsuximide is of little, if any, value for the control of grand mal seizures. Methsuximide is apparently more effective when used in conjunction with other drugs; there is no contraindication to using it in combination with any of the other anticonvulsants. The most effective combinations, however, remain to be determined.

Dosage

Methsuximide is administered orally. The optimal dose for controlling seizures must be carefully determined for each individual patient. However, 300 mg. per day is suggested for initiating treatment. Then, if necessary, the dosage may be gradually increased over a period of several weeks, until a total daily dose up to 1.2 Gm. is reached.

Preparations

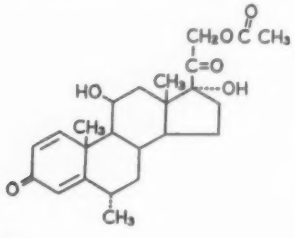
Capsules 300 mg.

Year of introduction: 1958.
Parke, Davis & Company cooperated by furnishing scientific data to aid in the evaluation of methsuximide.

J.Am.Med.Assoc. *171*:178/1506 (Nov. 14) 1959.

Methylprednisolone Acetate — Depo-Medrol®

Methylprednisolone Acetate (Depo-Medrol) is 6α-methylprednisolone-21-acetate.—The structural formula of methylprednisolone acetate may be represented as follows:



Actions and Uses

Methylprednisolone acetate shares the actions and uses of the parent compound, methylprednisolone. (See the monograph on methylprednisolone in New and Nonofficial Drugs.) Aqueous suspensions of the drug are suitable for intrasynovial and soft tissue injection and thus may be used for the local treatment of rheumatoid arthritis, osteoarthritis, tendinitis, bursitis, and other conditions that are responsive to the anti-inflammatory action of gluco-corticoids. When used in this manner, the effect of methylprednisolone acetate is comparable in intensity and duration of action to that of other relatively insoluble steroid compounds, but slower in onset and of longer duration than that of the highly soluble salts. In addition, methylprednisolone acetate may be administered by intracutaneous or intralesional injection for the treatment of susceptible dermatological conditions. The drug is also suitable for systemic therapy and, when administered intramuscularly, may be expected to produce the effects of orally administered methylprednisolone. It has been incorporated in retention enemas, which have been tried experimentally in the management of ulcerative colitis; although not all patients respond favorably, some experience marked improvement.

Methylprednisolone acetate apparently produces little or no pain or irritation after injection into the joint spaces or soft tissues. Systemic effects after local use have not been reported. Rapid settling of the drug may occur, however, if its suspensions are mixed with solutions of local anesthetics; such mixtures are rarely required. Intra-articular or other injection for local effect is contraindicated in the presence of acute infection. Precautions, contraindications, and undesirable effects described for the oral use of methylprednisolone are applicable also to the intramuscular use of methylprednisolone acetate.

Dosage

Methylprednisolone acetate is administrated by intramuscular, intrasynovial, or soft tissue injection. For intra-articular injection, the dose required varies with the size of the joint and the degree of inflammation. For large joints, such as the knee, ankle, or shoulder, 20 to 80 mg. may be required; for the elbows or wrist, 10 to 40 mg., and for smaller joints, 4 to 10 mg. In the management of bursitis, tendinitis, or epicondylitis, 4 to 30 mg. is administered in a single injection, which may be repeated as required. For local injections in dermatological conditions, doses of 20 to 60 mg., depending on the size of the lesion, may be employed.

For systemic effects, such as in rheumatoid arthritis, methylprednisolone acetate is administered intramuscularly in a single dose of 40 to 120 mg. per week. If daily administration is preferred, the dose is approximately the same as the oral dose of methylprednisolone.

Preparations

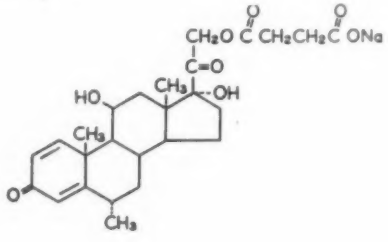
Suspension (injection) 40 mg. in 1 cc., 200 mg. in 5 cc.

Year of introduction: 1959.
The Upjohn Company cooperated by furnishing scientific data to aid in the evaluation of methylprednisolone acetate.

J.Am.Med.Assoc. *171*:167/1691 (Nov. 21) 1959.

Methylprednisolone Sodium Succinate — Solu-Medrol®

Methylprednisolone Sodium Succinate (Solu-Medrol) is sodium 6α-methylprednisolone-21-succinate.—The structural formula of methylprednisolone sodium succinate may be represented as follows:



Actions and Uses

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. Because it is highly soluble and can be administered in small volumes of diluent, it is useful for parenteral injection in situations in which a prompt and intense hormonal effect is indicated. Equimolar amounts of parenterally administered methylprednisolone sodium succinate and orally administered methylprednisolone have the same biological activity.

Parenterally administered methylprednisolone sodium succinate is intended primarily for short-term emergency therapy. Under these circumstances, typical steroidal side-effects are not likely to become a problem. The drug is subject to the same contraindications as other systemically administered agents of this class. (See the general statement on gluco-corticoids in New and Nonofficial Drugs.)

In a small series of patients, methylprednisolone sodium succinate has been administered rectally in the form of retention enemas for the management of less severe cases of ulcerative colitis. Results have been promising. Thus, in the majority of cases, clinical improvement has been noted within three days after institution of therapy; favorable proctoscopic changes have been observed within one week. These results suggest that, by the rectal route, improvement may be anticipated more promptly than when orally given steroids are employed. However, considerably more clinical experience with this relatively untried procedure is necessary before it can be routinely advised.

Dosage

For parenteral therapy, methylprednisolone sodium succinate is administered by intravenous or intramuscular injection or by intravenous infusion. The intravenous route is preferred for initial emergency therapy. The usual dose for intravenous or intramuscular injection is 40 mg.; frequency of administration is governed by clinical response. For intravenous infusion, a solution containing 40 mg. in 1 cc. is diluted with appropriate volumes of 5 percent dextrose in water, isotonic saline solution, or 5 percent dextrose in isotonic saline solution, and administered by slow drip.

For rectal use in patients with ulcerative colitis, solutions containing 40 to 120 mg. are added to varying amounts of water and administered as retention enemas three to seven times weekly for periods of two or more weeks.

Preparations

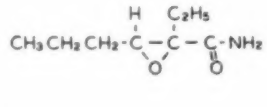
Powder (injection) 40 mg. with 1 cc. of sterile diluent.

Year of introduction: 1959.
The Upjohn Company cooperated by furnishing scientific data to aid in the evaluation of methylprednisolone sodium succinate.

J.Am.Med.Assoc. *171*:168/1692 (Nov. 21) 1959.

Oxanamide — Quiactin®

OXANAMIDE (Quiactin) is 2-ethyl-3-propylglycidamide.—The structural formula of oxanamide may be represented as follows:



Actions and Uses

Oxanamide, which resembles meprobamate in its action on the central nervous system, produces a calming effect that is often useful in the management of psychoneuroses, the major psychoses, and aberrations of behavior associated with cerebral arteriosclerosis and other disorders. The drug is most effective when the predominant symptom is anxiety or tension, regardless of the underlying cause or clinical diagnosis. Patients who respond may display an improvement in general behavior, lessening of anxiety and depression, and an increased interest in the environment. Psychosomatic symptoms, such as tension headache, may also respond to oxanamide. Its use in psychotic patients may permit a reduction in the frequency of electroshock therapy and may facilitate social readjustment by decreasing quarrelsomeness and irritability; a few patients show sufficient improvement to allow paroling from institutions. Oxanamide has not been employed for quieting acutely disturbed patients and, because of the relative mildness of its central depressant action, is probably not suitable for this purpose. A definite assessment of the relative efficacy of oxanamide, in comparison with other similar drugs, must await further clinical testing; that it is more efficacious than older drugs has not been established.

Pharmacology

Oxanamide is well absorbed after oral administration. In animals, only 10 percent of a single dose is excreted in the urine; the fate of the remainder is unknown. The disposition of the drug in man has not been determined; no evidence of cumulation has followed repeated administration of usual doses to human patients.

Laboratory studies indicate that oxanamide is primarily a central nervous system depressant. It appears to be an internuncial neuronal blocking agent, to inhibit polysynaptic reflexes, and, by means of these central actions, to produce a degree of skeletal muscle relaxation. Large doses have also been reported to exert a hypnotic effect similar to that of short-acting barbiturates. The precise pattern of activity of oxanamide on the central nervous system, including possible interaction with transmitter substances, has not been determined.

Side-effects.—Oxanamide is remarkably free from serious toxicity. No adverse effects on renal, hepatic, or hematopoietic function have been reported. Drowsiness may occur but is infrequent and usually appears only after large doses. In normal individuals, doses of 800 mg. do not alter reaction time or performance in complex tasks such as those involved in driving. Oxanamide has not, as yet, been reported to cause habituation or addiction. Withdrawal symptoms have not been seen after discontinuance of therapy. However, present experience is much too limited to justify a definite assumption that the drug is devoid of addicting potentiality.

Dosage

Oxanamide is administered orally. The usual dose is 400 mg. given four times daily, but this should be adjusted to meet the needs of the individual patient. For sedative effect, 800 mg. may be given at bedtime.

Preparations

Tablets 400 mg.

Year of introduction: 1958.
The Wm. S. Merrell Company cooperated by furnishing scientific data to aid in the evaluation of oxanamide.

J.Am.Med.Assoc. *171*:169/1693 (Nov. 21) 1959.

Penicillinase — Neutrapen®

PENICILLINASE (Neutrapen) is specially purified enzyme preparation obtained by fermentation from cultures of a strain of Bacillus cereus. A unit of penicillinase is defined as that amount which, in vitro, inactivates one unit of penicillin per minute at 25 C at a pH of 7.0.

Actions

Penicillinase is an enzyme preparation proposed for use in the treatment of reactions to penicillin. The enzyme catalyzes the hydrolysis of the β-lactam ring of penicillin; the resulting product is penicilloic acid, which is biologically and, presumably, antigenically inactive. Penicillinase is pro-

duced not only by B. cereus, but also by certain strains of Escherichia coli, many strains of staphylococci, and by a large variety of other bacteria. It probably contributes significantly to the resistance of some, but not all, penicillin-insensitive micro-organisms.

Within a short time after injection of penicillinase, penicillin can no longer be detected in the blood, even when blood levels prior to this injection are quite high. Experimental studies in rabbits have shown that, when 5,000 units of penicillinase were injected simultaneously with 100,000 units of either potassium penicillin G or procaine penicillin G, blood levels of penicillin returned to zero within one hour after injection. When the dose of penicillinase was increased to 10,000 units, no penicillin was detectable at any time after injection. The duration of action of a single injection of penicillinase was found to be about four days. Similar results have been reported in guinea pigs. In human patients who had received 800,000 units of procaine penicillin G, a single injection of 100,000 to 800,000 units of penicillinase was found to completely eliminate penicillin from the blood within one hour. No penicillin could be detected in the blood for periods of four to seven days, despite the fact that injections of penicillin were continued twice daily.

Although penicillinase has had only limited clinical trial in the treatment of reactions to penicillin, early reports, based on uncritical studies, are favorable. Some response to treatment may occur within six hours but usually is seen only after one to four days. The various manifestations of delayed reactions to penicillin, including skin eruptions, urticaria, arthralgia, asthma, and fever, are reported to respond favorably to the enzyme. Reactions to procaine penicillin G are said to clear as quickly as those to the longer-acting benzathine penicillin G. Results are best when the penicillinase is administered within 24 hours after the reaction has begun.

Uses

Penicillinase may be employed for the treatment of slowly developing or delayed penicillin reactions. Adjunctive use of more rapidly acting drugs may prove necessary or advisable, however. It should also be remembered that a considerable period of time will be required for recovery from physical changes associated with penicillin reactions, even after all traces of penicillin are removed from the body.

Anaphylactic reactions to penicillin should first be controlled by epinephrine and other rapidly acting agents; penicillinase may then be given to eliminate the circulating antigen, if desired. Reliance on penicillinase alone in such reactions is contraindicated, since effects of the enzyme are evident only after several hours.

The use of penicillinase as a diagnostic agent to distinguish between penicillin reactions and other syndromes must be regarded as experimental. Similarly, its possible value in preventing reactions in patients who are known to be sensitive to penicillin and who are given injections of vaccines or other penicillin-containing products has not been established. Neither of these uses (diagnostic or prophylactic) is recommended for routine application at the present time.

The use of penicillinase is an interesting approach to the treatment of penicillin reactions. Destruction of the causative agent rather than mere suppression of symptoms is certainly logical and desirable on theoretical grounds. At the present time, however, the efficacy of penicillinase has not been established. Recovery from penicillin reactions often occurs spontaneously within a few days, even when no treatment is administered. For this reason, assessment of the value of any agent used for treatment of these reactions requires the most carefully designed clinical trials. Such trials of penicillinase have not yet been done; no double-blind study has been reported.

Side-effects.—Experimental animal studies indicate that penicillinase has a remarkably low acute toxicity. Doses as high as 10,000,000 units per kilogram of body weight given intramuscularly are well tolerated. Chronic toxicity studies revealed no adverse effects from daily injections for a period of six weeks. However, since penicillinase is an enzyme and, therefore, almost certainly a protein, it must be regarded as an antigen. In addition, all the other dangers attending the injection of a foreign protein will probably be noted. Indeed, several severe reactions which closely followed the injection of penicillinase in human patients have already been reported. The symptoms of these reactions suggested an acute anaphylactoid response, although none of the patients had previously received penicillinase. Less serious reactions that have been observed in clinical usage include local pain at the site of injection, weakness, malaise, a morbilliform rash, and a mild, self-limited febrile reaction.

Dosage

Penicillinase is administered by deep intramuscular injection. It should be freshly dissolved in sterile distilled water just prior to use. The concentration of penicillinase in the solution should be 400,000 units per cubic centimeter. The proposed dose for adults is 800,000 units (2 cc. of such solution). The dose may be repeated at intervals of three to seven days if necessary. It is claimed that two injections are usually sufficient to afford permanent relief from the symptoms of a single reaction.

Preparations

Powder (injection) 800,000 units.

Year of introduction: 1958.

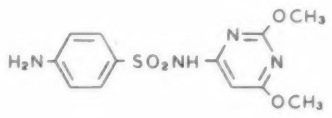
SchenLabs Pharmaceuticals, Inc., cooperated by furnishing scientific data to aid in the evaluation of penicillinase.

J.Am.Med.Assoc. 171:127/1105 (Oct. 24) 1959.

Sulfadimethoxine

Madribon®
Madriqid®

SULFADIMETHOXINE (Madribon, Madriqid) is N^1-(2,6-dimethoxy-4-pyrimidyl sulfanilamide.—2,4-Dimethoxy-6-sulfanilamido-1,3-diazine.—The structural formula of sulfadimethoxine may be represented as follows:



Actions and Uses

Sulfadimethoxine, like sulfamethoxypyridazine, is characterized by slower renal excretion and more prolonged blood levels than most other sulfonamides. However, it resembles other members of this group in its antibacterial spectrum, side-effects, and indications for use. (See the general statement on sulfonamide compounds in New and Nonofficial Drugs.)

Oral administration of sulfadimethoxine produces peak blood levels within four to eight hours, depending on the size of the dose. After administration of 2 Gm. initially, followed by 1 Gm. daily, peak levels are maintained on a plateau. Larger doses, however, may produce cumulation and a gradual rise in the blood sulfonamide concentration.

Approximately 85 percent of the sulfadimethoxine in the blood is in the active form; 10 percent is present as the acetyl derivative, and the remainder is a glucuronide. The exact structure of this glucuronide, as well as the site of its metabolic formation, is unknown. Antibacterial activity of the metabolite cannot be demonstrated.

Sulfadimethoxine is excreted in the urine. Approximately 5 percent appears in the unchanged form, 15 percent is

acetylated, and 80 percent appears as a glucuronide. Roughly one-half of a single dose of 2 Gm. can be recovered from the urine within 48 hours after administration. On a constant drug intake of 1 Gm., about 80 percent of the drug is excreted daily. Sulfadimethoxine and its acetyl derivative have exceedingly low solubilities in acid solutions, but the solubility of the major excretion product, the glucuronide, is quite high, exceeding 2,000 mg. per 100 cc. at a pH of 6.0.

Sulfadimethoxine has been employed successfully for the treatment of certain bacterial infections of the soft tissues and respiratory tract. Results in urinary tract infections have also been satisfactory, despite the fact that the sulfonamide is present in the urine largely as the inactive glucuronide.

Side-effects observed with the use of sulfadimethoxine, such as nausea, vomiting, and skin eruption, are essentially the same as those previously reported for other sulfonamides. No reports of crystalluria, hepatic damage, or blood dyscrasias have yet appeared. As with other sulfonamides, administration of sufficient fluid to maintain a daily urine output of 1,000 cc. or more seems advisable; when the drug is given over a prolonged period, hematological studies should be performed at regular intervals.

Dosage

Sulfadimethoxine is administered orally. Because of its relatively slow excretion, a single daily dose is sufficient to maintain adequate blood levels. For mild infections in adults and children weighing 80 lb. (36.3 kg.) or more, an initial dose of 1 Gm., followed by 500 mg. daily, may be tried. For more severe infections, doses up to twice as great may be necessary. In children weighing less than 80 lb., doses of 12.5 to 25 mg. per pound of body weight, depending on the severity of the infection, are suggested for initiating therapy. One-half of the original dose is then given every 24 hours.

The appropriate daily doses of sulfadimethoxine may also be given in divided amounts; one-fourth of the daily dosage previously stated is administered every six hours.

Preparations

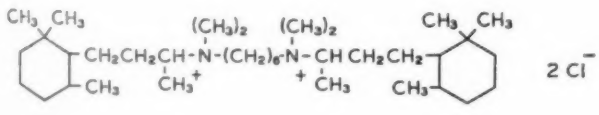
Capsules 125 mg.; suspension (oral) 50 mg. per cc.; suspension (oral drops) 250 mg. per cc.; tablets 500 mg.

Year of introduction: 1958.
Hoffmann-LaRoche Inc. cooperated by furnishing scientific data to aid in the evaluation of sulfadimethoxine.

J.Am.Med.Assoc. 171:169/1693 (Nov. 21) 1959.

Triclobisonium Chloride — Triburon® Chloride

TRICLOBISONIUM CHLORIDE (Triburon Chloride) is N,N'-bis[1 - methyl-3-(2,2,6,-trimethylcyclohexyl) propyl]-N,N'-dimethyl-1,6-hexanediamine bis(methochloride).—The structural formula of triclobisonium chloride may be represented as follows:



Actions and Uses

Triclobisonium chloride, a bisquaternary ammonium compound, is an antibacterial agent; applied topically, it is used in the management of superficial skin infections and vaginitis. The organisms most sensitive to its effects, in vitro, are strains of Staphylococcus pyogenes var. aureus, including some that are resistant to commonly employed antibiotics, Streptococcus pyogenes. Diplococcus pneumoniae, Listeria monocytogenes, and Salmonella typhi. In higher concentrations, it inhibits the growth of Pseudomonas aeruginosa, some fungi, and Trichomonas vaginalis. Some strains of Escherichia coli are moderately sensitive, whereas others are almost completely resistant.

Despite its antimicrobial activity in vitro, the efficacy of triclobisonium chloride in the treatment of superficial infections caused by the aforementioned organisms is not clearly established. Early trials have been uncontrolled studies in which no systematic comparison with other quaternary ammonium compounds or with other local anti-infectives, including topically applied antibiotics, was attempted; no double-blind study has been reported. Nevertheless, early clinical reports, especially when the drug was used in the treatment of impetigo contagiosa, are favorable; the drug is said to accelerate recovery in acute folliculitis, furunculosis, infectious eczematoid dermatitis, and other primary pyodermata and secondary infected dermatoses. It is also reported to be helpful in the management of Trichomonas vaginalis vaginitis, and, to a lesser extent, monilial, and so-called non-specific vaginitis. Fungus infections of the skin respond poorly. Thus, if subsequent properly designed clinical experimentation substantiates these preliminary impressions, triclobisonium chloride can be regarded as a useful adjunct in the management of superficial infections caused by susceptible organisms.

Topical application of triclobisonium chloride to the skin produces some degree of primary irritation in about 1 percent of patients; others exhibit signs of sensitization after repeated application. Although, in one study utilizing the closed patch technique, about 2 percent of normal human subjects developed allergic responses to triclobisonium chloride, fortunately the incidence of such reactions in the clinical use of the drug has been somewhat lower. Experimental instillation of a 1 percent solution into the eye of a rabbit provoked a slight erythema which subsided within 48 hours and left no residual damage; 0.1 percent solutions produced no irritation. Ointments and solutions of triclobisonium chloride produced no untoward effect when applied to the vagina of the rabbit. Local application of the drug has not produced toxic effects attributable to systemic absorption either in man or in experimental animals.

See also the general statement on cationic agents in the section on disinfectants and antiseptics in New and Nonofficial Drugs.

Dosage

Triclobisonium chloride is applied topically or intravaginally. For the treatment of pyogenic diseases of the skin, a cream or ointment containing 0.1 percent triclobisonium chloride is applied to the affected area three or four times daily and is rubbed in gently. If the drug is applied to extensive or acutely inflammed areas, the patient should be carefully observed for evidence of systemic toxicity, even though such effects have not yet been reported. Because of the occurrence of primary irritation and allergic reactions in some patients, unsupervised use of the drug is not recommended. For the treatment of vaginitis, a single application of triclobisonium cream (0.1 percent) is introduced into the vagina each night.

Preparations

Cream (topical, vaginal) 0.1 percent; ointment (topical) 0.1 percent.

Year of introduction: 1959.
Hoffmann-LaRoche, Inc., cooperated by furnishing scientific data to aid in the evaluation of triclobisonium chloride.

J.Am.Med.Assoc. 171:176/1504 (Nov. 14) 1959.

POSITIONS

in hospital pharmacy

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The Personnel Placement Service is operated without charge for the benefit of hospitals and pharmacist members of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The ultimate purpose is the improvement of pharmaceutical services in hospitals, by more adequately fulfilling hospital pharmacy personnel needs and by locating positions which provide challenging opportunities for pharmacists who have indicated an interest in a hospital career.

By participating in the service, the hospital indicates a desire to achieve a pharmaceutical service which meets the Minimum Standard for Pharmacies in Hospitals. A description of the position should be submitted to the Division of Hospital Pharmacy on the forms provided. The hospital will receive applications directly from the applicant. The hospital agrees to reply to each application received and to notify the Division of Hospital Pharmacy when the position is filled.

The pharmacist, by participating, agrees to submit a Personnel Placement Service Information Form to the Division of Hospital Pharmacy. The applicant will then be notified of openings listed with the Service as they become available and can negotiate directly with the hospital if he is interested. It is agreed that the Division of Hospital Pharmacy will be notified as soon as a position is accepted.

A listing of positions open and wanted will be made regularly in the AMERICAN JOURNAL OF HOSPITAL PHARMACY without charge. Neither the name of the hospital offering the position nor the name of the applicant will be listed, except by code. All inquiries should be directed as shown below, including the code number.

Address all inquiries to
Division of Hospital Pharmacy
2215 Constitution Avenue, N. W.
Washington 7, D.C.

positions open

PHARMACIST—Must be registered for 154 bed Government general hospital primarily for the care of Samoan people. Complete charge of the pharmacy, responsible for dispensing, charges, inventory and ordering through local Medical supply dept. Forty hour week with occasional after hour calls. Free medical and hospital care. Transportation furnished. Ten weeks paid leave at the end of two year contract. Renewable with increase if mutually agreeable. Male or female, single person preferred. Write airmail giving training and experience to: Personnel Officer, Government of American Samoa, Pago Pago, American Samoa.

CHIEF PHARMACIST—264 bed general hospital located in Texas. Plans and directs pharmacy policies, compounds and dispenses medicines, purchases supplies and materials, maintains records and prepares periodical reports. Must be eligible or have M. S. degree. Forty hour week, 2 weeks vacation. Retirement, sick leave. Hospitalization and life insurance available at no cost to employee. PO-177

CHIEF PHARMACIST—376 (expanding to 600) bed general hospital. Pharmacist will supervise and handle administrative duties in large active pharmacy which has 9 employees. Must have B. S. in Pharmacy, New York State registration or be eligible for licensure. Prefer applicant with at least five years hospital pharmacy experience with some supervisory ability. Forty hour week, 4 weeks vacation, insurance, pension plan. PO-176

ASSISTANT CHIEF PHARMACIST—300 bed hospital located in Pa. Duties include prescription dispensing and compounding, manufacturing, narcotic inventory control, and maintaining stock preparations. Prefer young man. PO-175

ASST. CHIEF AND/OR STAFF PHARMACIST—330 bed voluntary general hospital located in Midwest. Duties include compounding and dispensing medications to inpatients, outpatients, and employees. PO-174

STAFF PHARMACIST—Outstanding opportunity in large, well-known hospital in the Mid-west. Duties include filling prescriptions and floor supply, and some bulk compounding. Eligible for registration in Minnesota; hospital experience preferred. PO-173

PHARMACIST—60 bed hospital located in southwest Colorado needs service of a competent pharmacist. Generous benefits include meals while on duty. Male or female. Excellent quarters available to a single female at very nominal fee in new nurse residency. PO-172

PHARMACIST—800 bed general hospital. Compounds and dispenses medications, sell proprietary medicines, sundries and allied supplies to both in and outpatients. Must be licensed in Indiana or eligible for licensure. Fifty hour week, 2 weeks vacation after 1 year, 3 weeks after 3 years and 4 weeks after 5 years, retirement program entirely free, liberal employee discounts. PO-171

STAFF PHARMACIST—290 bed general medical and surgical city hospital. Duties include compounding, dispensing, manufacturing, and assisting in the purchasing of supplies. Prepares reports and maintains records. Furnishes information concerning medications to physicians and nurses. In absence of associate pharmacist will assist with special duties as assigned by chief pharmacist. Male or female between 23-45 years of age. Ohio registration required. Hospital pharmacy internship preferred. Forty hour week, 2-3 weeks vacation, 15 days sick leave, retirement plan, credit union, 6 holidays, Blue Cross available. PO-170

STAFF PHARMACIST—200 bed general hospital. Duties include compounding, dispensing and manufacturing. Applicant must have B. S. in Pharmacy and registered in Conn. Recent graduate acceptable. Forty-four hours per week, two weeks' vacation, pension plan and hospitalization. PO-168

ASST. CHIEF PHARMACIST—102 bed general hospital located in Oregon. Pleasant surroundings in college city of 8,000-20,000 students. Male or female. Must be registered. Forty hour week, 2 weeks' vacation, holidays and sick days. PO-166

ASST. CHIEF PHARMACIST—350 bed general hospital. Assist in training and supervision of employees and in plans and projects of dept. Direct dept. in absence of chief pharmacist. Registration in Ohio and B. S. degree required. Only male considered, must be over 21 years of age. Forty hour week, 2 weeks' vacation, Social Security, paid holidays, group hospitalization, sick leave. PO-165

STAFF PHARMACIST—100 bed general hospital located in Texas. Assume personal responsibility for accurate filling of prescriptions and supplies, assist in inspecting drugs in nursing stations, replace stock taken from night emergency container, inspect and refill ophthalmic solution trays from operating room, emergency room and central supply. Female preferred. Must be registered or eligible for registration in Texas. Forty hour week, 2 weeks vacation after one year, paid holidays, 7 days sick leave. PO-164

ASST. CHIEF PHARMACIST—280 bed general hospital. Duties include filling prescriptions and medicine orders from various units, supervise pharmacy clerks, assume administrative responsibility when chief pharmacist is absent. Forty-four hour week, sick leave and six paid holidays. Must be registered in Ill. PO-161

ASST. CHIEF PHARMACIST—293 bed general hospital. Dispensing drugs to nursing stations, filling special orders for patients, ordering stock, keeping records and some manufacturing. Forty hour week, 2 weeks' vacation, 12 days sick leave, 6 holidays, meals while on duty, free hospital care. Must be registered in Md. PO-160

ASST. CHIEF PHARMACIST—235 bed general hospital located 7 miles from Akron, Ohio. Hospital expanding to 310 beds in 1960, pharmacy expanding to serve 500 beds. Filling prescriptions, small volume of manufacturing. Must assume responsibility for pharmacy in the absence of chief pharmacist. Forty hour week, 2 weeks' vacation, hospitalization insurance paid for employee after 6 months probationary period, paid sick leave, 6 paid holidays. PO-159

CHIEF PHARMACIST—103 bed general hospital. Purchasing, receiving and issuing of pharmacy supplies. Taking inventory once a year. Filling out various reports necessary to operation of dept., etc. Must be registered in Wash. State. Forty hours per week, 2 weeks' vacation, 7 paid holidays, 1 sick day per month cumulative to 48, Blue Cross Insurance available. PO-158

STAFF PHARMACIST—269 bed nonprofit general hospital located in Calif. Duties include filling ward orders, individual prescriptions, outpatient prescriptions and narcotic orders. Applicant must have B. S. in pharmacy, 1 year's experience or perferably hospital pharmacy internship. Willingness to work week ends and nights as required. Male or female. Forty to forty-eight hour week, two weeks' vacation after one year, 6 paid holidays, 12 days sick leave, hospital insurance plan. PO-157

CHIEF PHARMACIST—190 bed general hospital located in Wis. Pharmacist will have complete control of the pharmacy, responsible for dispensing, charges, inventory and purchasing. Work with Medical Staff to formulate policies for dept. with administrative approval. Capable of cooperating with the Medical Staff, helping the Medical Staff keep abreast of advances in the field, and guiding and directing the Nursing Staff in their usage of drugs. Thirty-six to forty-four hour week, two weeks' vacation after one year, Municipal Pension Plan, insurance, 10 days sick leave per year accumulative to 30. Must be registered in Wis. PO-156

SUPERVISOR OUTPATIENT PHARMACY OR STAFF PHARMACIST—236 open bed general state hospital located in Ark. Supervisor's duties include some teaching of pharmacy students, supervise one other pharmacy and administer this subdivision which fills about 200 prescriptions daily. Must be an especially intelligent and well trained pharmacist preferably with an internship in hospital pharmacy. STAFF PHARMACIST rotates among the various subdivisions of the hospital pharmacy: outpatient pharmacy, inpatient pharmacy, non sterile manufacturing and sterile manufacturing. Should be a good pharmacist, intelligent, interested in hospital pharmacy professionally. Forty hour week, vacation, 6 paid holidays per year, opportunity to learn in one of the most active hospital pharmacy depts. in the country, after 2 years participate in retirement program which provides essentially a 6% increase in salary, close relationships with schools of pharmacy, medicine and nursing. PO-154

STAFF PHARMACIST—215 bed general hospital. Compound and dispense drugs, manufacture pharmaceuticals and assist in all other pharmaceutical duties in the pharmacy. B. S. required. Must be eligible for licensure in Pa. Forty hour week, three weeks' vacation, 7 holidays, 10 days paid sick leave, annual physical examinations, merit salary increases. PO-152

ASST. PHARMACIST—250 bed general hospital. Forty hour week, 2 weeks' vacation, sick leave and 6 paid holidays per year. Must be registered in N. C. PO-150

STAFF PHARMACISTS—Unique, new 400 bed general private hospital where pharmacists join the doctor-nurse team by working in a dispensing unit location on each 100 bed nursing unit or in the central pharmacy. The dispensing unit personnel have responsibility for providing drugs, oxygen, dressing trays, I.V. solutions and similar items. A total of sixteen staff pharmacists is required to staff the hospital. Applicants must be eligible for registration in Calif. Excellent opportunity; generous benefits. PO-148

ASST. CHIEF PHARMACIST—250 bed general hospital located in N. Y. Male preferred. Registration in N. Y. required. Ability to pass N. Y. State Civil Service examination. Duties include filling ward orders, patient prescriptions, checking stock and small volume parenteral solution manufacturing. Forty hour week, 3 weeks' vacation, annual sick leave, 7 paid holidays, retirement plan, group insurance available. Located outside city. Some housing available on premises. PO-146

CHIEF PHARMACIST—150 bed general hospital located in N. M. To assume complete charge of purchasing and distributing drugs. PO-134

STAFF PHARMACIST—75 bed general, private hospital located in Ind. State registration required. Male or female. PO-131

CHIEF PHARMACIST—185 bed private nonprofit hospital located in Va. Prefer applicant with hospital pharmacy internship and one year's experience. PO-126

CHIEF PHARMACIST—60 bed mission hospital operated by Presbyterian National Missions; extensive outpatient dept.; on Navajo Indian Reservation near Gallup, N. M. Qualified to register in Ariz.; single man or woman, challenged by service rather than benefits. PO-122

ASST. CHIEF PHARMACIST—425 bed general hospital. Duties include dispensing and supervision of special projects. Prefer male applicant with internship in hospital pharmacy. Unique opportunity to obtain experience. PO-115

STAFF PHARMACIST—215 bed general hospital expanding to 35 more beds. N. Y. registration required as well as hospital experience. Forty hour week, 2 weeks' vacation. PO-104

CHIEF PHARMACIST—400 bed hospital located in the Midwest. Complete responsibility for the pharmaceuticals of a normal modern hospital including drug purchasing and departmental staffing. Staff presently consists of chief pharmacist, five staff pharmacists, clerk-typist, stock man, and several part-time workers. Salary to be based upon training and experience. PO-99

STAFF PHARMACIST—500 bed general hospital located in Okla. B. S. required. Forty hour week. PO-95

ASST. CHIEF PHARMACIST—315 bed general hospital. Registration in Iowa required. Experience desirable. Forty hour week, 2 weeks' vacation. PO-92

ASST. CHIEF PHARMACIST—237 bed general hospital in West Va. Female desired. Forty-four hour week, 2 weeks' vacation. PO-77

STAFF PHARMACIST—335 bed hospital located in Fla. Duties include responsibilities in outpatient dept. and parenteral solution room. Forty hour week, 2 weeks' vacation. One meal daily. PO-75

CHIEF PHARMACIST—88 bed hospital located in Pa. Planning expansion to 125 beds for general patients and 40 beds for chronic patients. Possibility for pharmacist to serve as Asst. Adm. in charge of Purchasing, Central Supply, and Store Room. Forty hour week, 2-4 weeks' vacation. Young man preferred. PO-59

ASST. CHIEF PHARMACIST—Large voluntary hospital located in Brooklyn. Must be eligible for registration in N. Y. Supervisory ability needed. Thirty-five hour week, 2 weeks' vacation, 10 days sick leave, 9 holidays. PO-51

positions wanted

STAFF PHARMACIST—Female, single. B.S. received at Purdue University in 1958. One and one-half years' hospital pharmacy experience. Registered in Indiana. Prefers to locate in East or Midwest. PW-219

CHIEF PHARMACIST—Male, single. B. S. received in 1952 at Mass. College of Pharmacy. Seven years' hospital pharmacy experience. Registered in Mass. Will locate anywhere. PW-218

STAFF OF CHIEF PHARMACIST—Male, single. B. S. received in 1952 at St. Louis College of Pharmacy. Two years' hospital pharmacy experience. Registered in Mo. Prefers West Coast, particularly Calif. PW-217

ASST. CHIEF OR STAFF PHARMACIST—Female, single. B. S. received at University of Saskatchewan in 1954. Three years' hospital pharmacy experience. Registered in Canada. Would prefer to locate in Southeastern or Western part of U. S. PW-216

CHIEF PHARMACIST—Male, married. Will receive M. S. in June, 1960 at the State University of Iowa. Served hospital pharmacy internship. Registered in Iowa, prefers to locate in the northern Middlewest. PW-215

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received in 1954 at the Southwestern State College in Okla. Served hospital pharmacy internship at Springfield City Hospital, Springfield, Ohio. Three years' hospital pharmacy experience. Registered in Okla., prefers to locate in Southwest. PW-214

ASST. CHIEF OR STAFF PHARMACIST—Male, married. B. S. received in 1954 at the University of Ga. Three years' hospital pharmacy experience. Registered in Ga. Prefers South. PW-213

CHIEF PHARMACIST—Female, single. B. S. Eleven years' hospital pharmacy experience. Prefers N. Y. Registered in N. Y. PW-212

CHIEF PHARMACIST—Male, married. PhG. and B. S. from Temple University. Prefers to locate in N. J. or Pa.; registered in both states. PW-211

STAFF PHARMACIST—Female. 1957 Graduate of the University of Buffalo College of Pharmacy. Registered in N. Y. Prefers to locate in the East. PW-171

CHIEF PHARMACIST—Male, married. M. S. received from Philadelphia College of Pharmacy and Science in 1958. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Presently completing military obligations. Will locate anywhere and will be available after July, 1960. Registered in Ohio. PW-210

ASST. CHIEF OR STAFF PHARMACIST—Female, single. B. S. Nineteen years' hospital pharmacy experience. Registered in Idaho, Alaska, Ohio and Oregon. Prefers Seattle, Wash. or Northwest section of country. PW-209

ASST. OR STAFF PHARMACIST—Female, single. Received B. S. from Texas Southern University in 1958. One year hospital pharmacy experience. Registered in Texas and Utah. Prefers West and East. PW-208

CHIEF PHARMACIST—Male, married. Received B. S. in 1957 from Brooklyn College of Pharmacy. Over one year hospital pharmacy experience. Registered in N. Y. and Ill. Prefers East. PW-207

ASST. CHIEF PHARMACIST—Male, single. B. S. received in 1956 from Columbia University College of Pharmacy. Served hospital pharmacy internship. Two years' hospital pharmacy experience. Registered in N. Y. Prefers New York City. PW-206

DIRECTOR OF PHARMACY SERVICE AND/OR CHIEF PHARMACIST—Male, married. Served hospital pharmacy internship and received M. S. in Hospital Pharmacy from the University of Mich. in June, 1959. Seven years' hospital pharmacy experience. Registered in Ill. and Mich. Will locate anywhere. PW-205

CHIEF PHARMACIST—Male, married. M. S. received from Philadelphia College of Pharmacy and Science in 1957. Served hospital pharmacy internship. Over four years' hospital pharmacy experience. Registered in Nebr., Ky., Iowa, and Pa. Prefers Midwest. PW-204

CHIEF PHARMACIST—Male, married. B. S. received from R. I. College of Pharmacy in 1953. Served hospital pharmacy internship from 1953-1955 at Jefferson Medical College Hospital. Four years' hospital pharmacy experience. Registered in Mass., R. I., Pa., and N. J. Prefers East. PW-203

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. B. S. received from St. Louis College of Pharmacy in 1946. Fifteen years' hospital pharmacy experience. Registered in Mo. and S. C. Prefers Southeast section of country. PW-202

CHIEF PHARMACIST—Male, married. Served internship. Over three years' hospital pharmacy experience. Registered in Ohio and Pa. Prefers South. PW-201

STAFF OR ASST. CHIEF PHARMACIST—Male, single. B. S. degree received from Duquesne University, Pittsburgh in 1959. Served two years' internship in hospital pharmacy. Registered in Pa. Will locate anywhere in U. S. PW-200

STAFF PHARMACIST—Female, single. B. S. Seven years' hospital pharmacy experience. Southwest section of country preferred. Registered in Ala. and Ga. PW-199

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received in 1952. One year's hospital pharmacy experience. Prefers Southeast section of country. Registered in Va. PW-198

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received at Philadelphia College of Pharmacy and Science, 1956. Two and one-half years' hospital pharmacy experience and six years' experience in manufacturing, mainly parenterals. Presently working in Nicaragua. Will locate anywhere in U. S. PW-197

PHARMACIST—Male, single. Hospital pharmacy experience B. S. Registered in Mo. and Ill. Will locate anywhere. PW-196

CHIEF PHARMACIST—Male, married. B. S. received in 1953. Four years' hospital pharmacy experience. Prefers Eastern part of country. Registered in Pa. and N. Y. PW-195

STAFF PHARMACIST—Female, single. B. S. Hospital pharmacy experience. Prefers central southern part of Canada. Registered in Philippines. PW-194

CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Pa., N. Y. and Fla. Prefers to locate in Pa. and N. Y. PW-193

CHIEF PHARMACIST—Male, single. A. B. degree received in 1949. Six years' hospital pharmacy experience. Prefers teaching hospital. Registered in Mass. and Conn. Desires to locate in East. PW-192

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Previous hospital pharmacy supervisory experience. Registered in N. Y., prefers to locate in New York City or vicinity. PW-191

STAFF PHARMACIST—Male, married. B. S. one year's hospital pharmacy experience. Registered in N. Y. and Fla. Prefers to locate in Fla. PW-190

CHIEF PHARMACIST—Male, single. B. S. Registered in Minn. and N. D. Prefers foreign job anywhere. PW-189

PHARMACIST—Male, single. B. S. received in 1956. One year's hospital pharmacy experience. Would prefer Chicago area. Registered in Mich. PW-186

CHIEF PHARMACIST—Male, married. M. S. Hospital experience. Prefers to locate in East. Registered in N. Y., Mich., N. J., and Fla. PW-184

PHARMACIST—Male, married. B. S. Three years' experience in Sudan Interior Mission Hospital. Prefers to locate in South particularly S. C. Registered in S. C. PW-183

STAFF OR ASST. CHIEF PHARMACIST—Female, single. B. S. Three years' hospital experience. Prefers to locate in Midwest. Registered in Mo. PW-181

PHARMACIST—Male, married. B. S. Interested in career in hospital pharmacy. Prefers to locate in East. Registered in N. Y. and Ill. PW-180

ASST. CHIEF OR CHIEF PHARMACIST—Male, B. S. received in 1954. Desires to locate in Mich., Ohio or Ill. Registered in Mich. PW-177

ASST. CHIEF OR STAFF PHARMACIST—Female, single. B. S. Registered in La. and Ohio. Prefers Ohio and Northern part of country. PW-176

CHIEF PHARMACIST—Male, married. B. S. Registered in Mo. and Kansas. Prefers Southeast or Southwest Section of country. Desires position with possibility of assuming administrative duties. PW-174

PHARMACIST—Butler University graduate with Ph.C. degree. Registered in Ill., Ky., Ind., and Oreg. Prefers to locate in Midwest. PW-173

PHARMACIST—Graduate Philadelphia College of Pharmacy and Science 1959; 22 months' hospital pharmacy experience. Registered in Pa. Desires position in the East. PW-172

PHARMACIST—Female. Graduate of the University of Idaho, 1954. Registered in Ill. Hospital experience. Prefers Chicago area. PW-166

CHIEF OR ASST. CHIEF PHARMACIST—Female. B. S. and M. S. Purdue University. Ten years' hospital pharmacy experience. Registered in Ind. and Ky. PW-164

PHARMACIST—Male. Registered in La. and Mo. Experienced. Prefers Midwest. PW-161

STAFF PHARMACIST—Male, married. Registered in N. Y. and N. J. Prefers New England. PW-157

ASST. CHIEF PHARMACIST—Male, single. Registered in N. Y. and Vt. Served hospital pharmacy internship, now employed part-time staff pharmacist. Prefers Eastern part of country. Has M. S., 4 years' hospital pharmacy experience. PW-154

CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Mass., Ill., Mo., Ky., Tenn., and Va. PW-150

PHARMACIST—Male, single. B. S. pharmacy, June 1959. Locate East. PW-149

ASST. CHIEF OR CHIEF PHARMACIST—Single, male. Registered in D. C., Ill., Md., and Pa. Graduate University of Pittsburgh in 1953, experience in research. Prefers North and East. PW-148

CHIEF PHARMACIST—Registered in Mo. and Ill. Ph.G. degree. Eight years' hospital pharmacy experience. PW-147

STAFF PHARMACIST—Male, single. Completed military requirements. Hospital pharmacy experience. Prefers East. PW-146

CHIEF PHARMACIST—Prefers N. Y. or N. J. area. Over 20 years' hospital experience as chief pharmacist and purchasing agent. Graduate St. John's University College of Pharmacy. Registered in N. Y. and N. J. PW-144

CHIEF PHARMACIST—Male, married. B. S. Conn. registration. Five years' hospital pharmacy experience. Prefers Northeast section of country. PW-140

PHARMACIST—Male, single. Registered in Conn. and N. J. Five years' hospital pharmacy experience. B. S. Prefers Conn. or Texas. PW-123

ASST. DIRECTOR OR DIRECTOR OF PHARMACY SERVICES—Male, single. B. S. Retail and five years' hospital experience. Registered in Ill. PW-119

CHIEF PHARMACIST—Female, single. Registered in Pa. and Ohio. Twelve years' experience as chief pharmacist. Desires to locate in Pa. or Ohio. PW-111

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February 1960

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